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(54) Title: GIPs, A FAMILY OF POLYPEPTIDES WITH TRANSCRIPTION FACTOR ACTIVITY THAT INTERACT WITH GOODPASTURE ANTIGEN BINDING PROTEIN

(57) Abstract: The present invention provides isolated GPBP-interacting 90 and 130 kDa polypeptides, and portions thereof (GIP90/130 polypeptides), antibodies to the GIP90/130 polypeptides, and pharmaceutical compositions thereof. The present invention also provides isolated GIP90/130 nucleic acid sequences, expression vectors comprising the nucleic acid sequences, and host cells transfected with the expression vectors. The invention further provides methods for detecting the GIP90/130 polypeptides or nucleic acid sequences, methods for inhibiting interactions between GPBP and GIP90/130 polypeptides, betwee pol k76 and GIP90/130 polypeptides or aggregation of GIP90/130 polypeptides, and methods for treating patients with autoimmune disorders or cancer.

GIPs, a Family of Polypeptides with Transcription Factor Activity that Interact with Goodpasture Antigen Binding Protein

Field of the invention

The present invention is in the general fields of molecular biology, cell biology, protein-protein interactions, autoimmunity, cancer, and drug discovery.

Background

Goodpasture antigen binding protein (GPBP) is a ubiquitous protein kinase with a M_r of 80-89 kDa that is preferentially expressed in tissues and cells that are common targets of autoimmune responses, such as the Langerhans islets (type I diabetes); the white matter of the central nervous system (multiple sclerosis); the biliary ducts (primary biliary cirrhosis); the cortical cells of the adrenal gland (Addison disease); striated muscle cells (myasthenia gravis); spermatogonium (male infertility); Purkinje cells of the cerebellum (paraneoplasic cerebellar degeneration syndrome); and intestinal epithelial cells (pernicious anemia, autoimmune gastritis and enteritis).

GPBP is expressed as two isoforms (GPBP and GPBPΔ26) which result from exon alternative splicing of the corresponding pre-mRNA. GPBP is the more active variant, and its expression is still more restricted to histological structures targeted by common autoimmune responses including human alveolar and glomerular basement membranes (Goodpasture disease). GPBP binds to and phosphorylates the human α3 NC1 domain of type IV collagen (α3(IV)NC1) also called the Goodpasture antigen (WO 00/50607), as this domain is the target of the pathogenic autoantibodies mediating the Goodpasture autoimmune response. Phosphorylation activates the α3(IV)NC1 domain for aggregation, a process that is catalyzed at least in part by GPBP and which comprises conformational isomerization reactions and disulfide-bond exchange (WO 02/061430).

An augmented expression of GPBP with respect to GPBPΔ26 has been associated with the production of non-tolerized, aberrant conformational versions of the human α3(IV)NC1 domain ("aberrant conformers") and the subsequent autoantibody production that causes Goodpasture disease (WO 02/061430). The evidence suggests that a similar pathogenic mechanism is involved in other autoimmune conditions, including cutaneous lupus erythematosus, pemphigus, pemphigoid and lichen planus, and that aberrant GPBP expression and autoimmune pathogenesis are related processes. Furthermore, GPBP is down-regulated in cancer cell lines (WO 00/50607), suggesting that the cell machinery harboring GPBP/GPBPΔ26 is also involved in signaling pathways that decrease cell division or induce cell death. These pathways could be up regulated during autoimmune pathogenesis to cause altered antigen presentation in individuals carrying specific MHC haplotypes, and down regulated during cell transformation to prevent autoimmune attack of the transformed cells during tumor growth.

Based on all of the above, there exists a need in the art to identify methods and reagents for modifying GPBP activity for use in treating autoimmune disorders and cancer.

Summary of the Invention

In one aspect, the present invention provides isolated GPBP-interacting 90 and 130 kDa polypeptides, and portions thereof (GIP90/130 polypeptides), antibodies to the GIP 90/130 polypeptides, and pharmaceutical compositions thereof. In a further aspect, the present invention provides isolated GIP90/130 nucleic acid sequences, expression vectors comprising the nucleic acid sequences, and host cells transfected with the expression vectors. The invention further provides methods for detecting the GIP90/130 polypeptides or nucleic acid sequences, methods for modifying interactions between GPBP and GIP90/130 polypeptides, aggregation of GIP90/130 polypeptides, and GIP90/130 polypeptide-mediated gene transcription, and methods for treating patients with autoimmune disorders or cancer.

Brief Description of the Figures

Figure 1 is a diagram of the exon-intron structure of the GIP90 genomic DNA as determined by BLAST search against Human Genome NCBI in May 20, 2002.

Figure 2 is a representation of differences between various GIP90/130 mRNA and polypeptide species.

Figure 3 is a sequence alignment of the full length GIP90/130 polypeptides and DOC1 and DOC1-related protein.

Figure 4 is the amino acid sequence of I-20. Residues in bold font are those identified as essential for interactions between GIP90/130 and GPBP; in small letters are other residues identified as participating in interaction between GIP90/130 and GPBP, but not essential; and underlined are the residues implicated in GIP90/130 aggregation.

DETAILED DESCRIPTION OF THE INVENTION

Within this application, unless otherwise stated, the techniques utilized may be found in any of several well-known references such as: *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), *Gene Expression Technology* (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press, San Diego, CA), "Guide to Protein Purification" in *Methods in Enzymology* (M.P. Deutshcer, ed., (1990) Academic Press, Inc.); *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press, San Diego, CA), *Culture of Animal Cells: A Manual of Basic Technique, 2nd Ed.* (R.I. Freshney. 1987. Liss, Inc. New York, NY), *Gene Transfer and Expression Protocols*, pp. 109-128, ed. E.J. Murray, The Humana Press Inc., Clifton, N.J.), and the Ambion 1998 Catalog (Ambion, Austin, TX).

As used herein, the term "GIP90/130" and "GIP90/130 polypeptide(s)" refers to the family of GPBP-interacting proteins that includes GIP90, GIP130a, GIP130b, and GIP130c, amino acid sequences derived therefrom, and includes both monomers and oligomers thereof.

As used herein, the term "GIP90" refers to the 90 kDa form of GIP, which consists of the amino acid sequence of SEQ ID NO:10, and includes both monomers and oligomers thereof.

As used herein, the term "GIP130a" refers to one of the 130 kDa forms of GIP, which consists of the amino acid sequence of SEQ ID NO:12, and includes both monomers and oligomers thereof.

As used herein, the term "GIP130b"refers to one of the 130 kDa forms of GIP, which consists of the amino acid sequence of SEQ ID NO:14, and includes both monomers and oligomers thereof.

As used herein, the term "GIP130c" refers to one of the 130 kDa forms of GIP, which consists of the amino acid sequence of SEQ ID NO:16, and includes both monomers and oligomers thereof.

The numbering of nucleotides and residues used below for GIP proteins refer to the GenBank accession number AF329092.

As used herein, the term "DOC proteins" or "DOC1 proteins" refers to down regulated in ovarian cancer-1 (DOC1) (Genbank accession number NM 014890) and DOC1-related protein (Genbank accession number BC027860). DOC1 and DOC1-related protein are derived from the same gene since they are identical in the homology region at nucleotide and amino acid levels

As used herein, the term "GPBP" refers to Goodpasture antigen binding protein, and includes both monomers and oligomers thereof, as disclosed in WO 00/50607.

As used herein, the term "GPBPΔ26" refers to the Goodpasture antigen binding protein alternatively spliced product deleted for 26 amino acid residues as disclosed in WO 00/50607, and includes both monomers and oligomers thereof.

As used herein pol κ means the primary protein product of the *POLK* as disclosed in WO 02/46378.

As used herein, pol κ76 means the 76 kDa alternatively spliced isoform product of the *POLK* as disclosed in WO 02/46378.

As used herein, "aggregation" refers to both self-aggregation of an individual GIP90/130 polypeptide, and aggregation of two or more different GIP90/130 polypeptides.

In one aspect, the present invention provides isolated GIP90/130 polypeptides. In one embodiment, the isolated GIP90/130 polypeptide comprises at least 6 amino acids of the amino acid sequence of SEQ ID NO:2, which is a unique 10 amino acid polypeptide (SYRRILGQLL) that is herein demonstrated to be essential for the interaction between GIP90/130 and GPBP (discussed in detail below), and is not present in DOC proteins. In further embodiments, the isolated GIP90/130 polypeptide comprises at least 7, 8, 9, or 10 amino acids of the amino acid sequence of SEQ ID NO:2. In still further embodiments, the isolated GIP90/130 polypeptide consists of at least 6, 7, 8, 9, or 10 amino acids of the amino acid sequence of SEQ ID NO:2. These polypeptides can be used, for example, to modify interactions between GPBP and GIP90/130 polypeptides or to raise antibodies that interfere with GPBP-GIP90/130 interaction.

In further embodiments, the isolated GIP90/130 polypeptide comprises and/or consists of the amino acid sequence of SEQ ID NO:4, which is the N-terminal region of GIP90/130a/c that is not present in DOC proteins (described in detail below), and which is encoded by exon II-IV and part of exon V (Figure 3). These polypeptides are thus useful, for example, to develop reagents, such as antibodies, that can distinguish between GIP90/130 and DOC proteins. This polypeptide includes sequences implicated in the interaction between GPBP and GIP90/130 (including SEQ ID NO:2), and thus can be used (or antibodies to the polypeptides can be used), for example, to modify interactions between GPBP and GIP90/130 polypeptides. This polypeptide also includes sequences implicated in GIP90/130 aggregation, and thus can further be used (or antibodies to the polypeptides can be used) to modify GIP90/130 aggregation. This polypeptide also includes sequences implicated in the transcriptional activity of GIP90/130 and thus the polypeptides, or antibodies derived therefrom, can be further used for modulating specific gene expression.

The polypeptides of the invention also include polypeptides comprising and/or consisting of the amino acid sequence of SEQ ID NO:6, which is referred to as I-20, a 265 amino acid polypeptide that is described in detail below. This polypeptide interacts more strongly with GPBP and pol κ76 than the full length GIP90/130 polypeptides, and aggregates more efficiently than the full length GIP90/130 polypeptides. Furthermore, I-20 does not induce gene transcription, in contrast to the full length GIP90/130 polypeptides. Therefore this polypeptide can be used (or antibodies to the polypeptides can be used), for example, to modify (a) interactions between GPBP and GIP90/130 polypeptides; (b) interactions between pol κ76 and GIP90/130 polypeptides; (c) GIP90/130 polypeptide aggregation; and (d) other functions of the GIP90/130 polypeptides, such as induction of gene transcription.

The polypeptides of the invention also include polypeptides comprising and/or consisting of the amino acid sequence of SEQ ID NO:8, which consists of the N-terminus of GIP90 to the end of I-20, and is encoded by exons II-IV and part of exon V up to the end of the I-20 coding sequence. This polypeptide includes sequences implicated in (a) the interaction between GPBP and GIP90/130 polypeptides, (b) GIP90/130 polypeptide aggregation, and (c) the transcriptional activity of GIP90/130 polypeptides, and thus the polypeptides, or antibodies derived therefrom, can be used, for example, to modify interactions between GPBP and GIP90/130 polypeptides, to modify GIP90/130 aggregation, and to modulate gene expression.

The polypeptides of the invention also include polypeptides comprising and/or consisting of the amino acid sequence of SEQ ID NO:10 (GIP90), SEQ ID NO:12 (GIP130a), SEQ ID NO:14 (GIP130b), or SEQ ID NO:16 (GIP130c). These full length polypeptides, described in more detail below, interact with GPBP and are capable of aggregation. These polypeptides can be used, for example, to modify GPBP-GIP90/130 interactions, to modify GIP90/130 aggregation, to modulate gene expression, as well as for other purposes described herein.

In a further embodiment, the isolated GIP 90/130 polypeptide comprises at least 8 amino acids of the amino acid sequence of SEQ ID NO:18, which is a unique 15 amino acid peptide that is present at the C-terminus of GIP90 and is not present in DOC proteins, GIP130a, GIP130b, or GIP130c, and thus can be used, for example, to generate reagents, such as antibodies, to distinguish GIP90 from other members of the GIP90/130 polypeptide family. Furthermore, the polypeptides, or antibodies thereto, can be used to specifically modify GIP90 self-aggregation. In further embodiments, the isolated GIP90/130 polypeptide comprises or consists of at least 9, 10, 11, 12, 13, 14, or 15 amino acids of the amino acid sequence of SEQ ID NO:18.

In a further embodiment, the isolated GIP90/130 polypeptide consists of at least 8 amino acids of the amino acid sequence of SEQ ID NO:20, which is a 30 amino acid polypeptide present within I-20 that has been implicated in the interaction of GIP90/130 with GPBP and also in GIP90/130 aggregation. In further embodiments, the isolated GIP90/130 polypeptide consists of at least 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 amino acids the amino acid sequence of SEQ ID NO:20. Thus, these polypeptides, or antibodies to the polypeptides, can be used, for example, to modify interactions between GPBP and GIP90/130 polypeptides. Furthermore, since this polypeptide is present in each of GIP90, GIP130a, GIP130b, GIP130c, and DOC1 proteins, these polypeptides, or antibodies thereto, can be used to generally modify aggregation of the GIP90/130 polypeptides and DOC1 proteins. Despite the fact that DOC1 proteins contain SEQ ID NO:20, they do not interact in a two hybrid assay with GPBP (see below), and thus SEQ ID NO:20, while implicated in the interaction of GIP90/130 polypeptides and GPBP, is not sufficient for GPBP interaction.

In a still further embodiment, the isolated GIP90/130 polypeptide comprises or consists of the amino acid sequence of SEQ ID NO:22, which is a unique 386 amino acid polypeptide that is present at the C-terminus of GIP130a but is not present in GIP90, is not wholly present in DOC1, and includes variations from GIP130b, GIP130c, and DOC1-

related protein, and thus can be used, for example, to modify GIP130a aggregation, and to generate reagents, such as antibodies, to distinguish GIP130a from other members of the GIP90/130 polypeptide family, and the DOC proteins. This region contains sequences that down-regulate GIP 90/130 interaction with GPBP which can be used to modify GIP90/130-GPBP interaction, or to generate reagents, such as antibodies for the same purposes.

In a still further embodiment, the isolated GIP90/130 polypeptide comprises or consists of the amino acid sequence of SEQ ID NO:24, which is GIP130a deleted from the N-terminus to the end of I-20. This polypeptide lacks critical regions of the GIP90/130 polypeptides implicated in GPBP interaction and induction of gene expression, and like the C terminus of GIP130b/c contains amino acid sequences that down-regulate interaction with GPPB. Thus, the polypeptides, or antibodies thereto, can be used, for example, to modify GPBP-GIP90/130 polypeptide interactions or to modify GIP90/130 polypeptide aggregation.

In a still further embodiment, the isolated GIP 90/130 polypeptide comprises or consists of the amino acid sequence of SEQ ID NO:26, which is a unique 7 amino acid polypeptide present at the C-terminus of GIP130a, and is not present in any of GIP90, GIP130b, GIP130c, and DOC proteins. Thus, these polypeptides can be used to produce reagents, such as antibodies, that are specific for GIP130a, and which can be used, for example, to specifically modify GIP130a aggregation.

In another embodiment, the isolated GIP90/130 polypeptide comprises at least 6 amino acids of the amino acid sequence of SEQ ID NO:28, which is a unique 10 amino acid polypeptide (LDKVVEKHKE) within I-20 that participates in interactions between GIP90/130 polypeptides and GPBP, is essential for GIP90/130 polypeptide aggregation, and is not present in DOC proteins. In further embodiments, the isolated GIP90/130 polypeptide comprises or consists of at least 7, 8, 9, or 10 amino acids of the amino acid sequence of SEQ ID NO:28. These polypeptides or antibodies raised against them can be used, for example, to modify interactions between GPBP and GIP90/130 polypeptides or to modify GIP90/130 polypeptide aggregation.

In another embodiment, the isolated GIP90/130 polypeptide consists of at least 6 amino acids of the amino acid sequence of SEQ ID NO:30, which is an 10 amino acid polypeptide (EEEQKATRLE) within I-20 that participates in interactions between GIP90/130 polypeptides and GPBP, is essential for GIP90/130 polypeptide aggregation, and is present in DOC proteins. In further embodiments, the isolated GIP90/130

polypeptide consists of at least 7, 8, 9, or 10 amino acids of the amino acid sequence of SEQ ID NO:30. These polypeptides or antibodies raised against them can be used, for example, to modify interactions between GPBP and GIP90/130 polypeptides or to modify GIP90/130 polypeptide aggregation. Furthermore, since this polypeptide is present in each of GIP90, GIP130a, GIP130b, GIP130c, and DOC1 proteins, these polypeptides, or antibodies thereto, can be used to generally modify aggregation of the GIP90/130 polypeptides and DOC1/DOC1-related proteins. Despite the fact that DOC1 proteins contain SEQ ID NO:20, they do not interact in a two hybrid assay with GPBP (see below), and thus SEQ ID NO:20, while implicated in the interaction of GIP90/130 polypeptides and GPBP, is not sufficient for GPBP interaction.

In another embodiment, the isolated GIP90/130 polypeptide comprises at least 8 amino acids of the amino acid sequence of SEQ ID NO:32, which is a unique 20 amino acid polypeptide (LDKVVEKHKESYRRILGQLL) within I-20 that contains essential residues for the interaction between GIP90/130 polypeptides and GPBP and for GIP90/130 polypeptide aggregation, and is not present in DOC proteins. In further embodiments, the isolated GIP90/130 polypeptide comprises or consists of at least 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids of the amino acid sequence of SEQ ID NO:32. These polypeptides can be used, for example, to modify interactions between GPBP and GIP90/130 polypeptides and to modify GIP90/130 polypeptide aggregation, or to raise antibodies that modify interactions between GPBP and GIP90/130 polypeptides and to modify GIP90/130 polypeptide aggregation.

In another embodiment, the isolated GIP90/130 polypeptide consists of at least 8 amino acids of the amino acid sequence of SEQ ID NO:34, which is a 50 amino acid polypeptide that is contained within I-20, contains regions essential for the interaction between GIP90/130 polypeptides and GPBP and for GIP90/130 polypeptide aggregation, and is present in DOC proteins. In further embodiments, the isolated GIP90/130 polypeptide consists of at least 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 amino acids of the amino acid sequence of SEQ ID NO:34. These polypeptides can be used, for example, to modify interactions between GPBP and GIP90/130 polypeptides and to modify GIP90/130 polypeptide aggregation, or to raise antibodies that modify interactions between GPBP and GIP90/130 polypeptides and to modify GIP90/130 polypeptide aggregation. Furthermore, since this polypeptide is present in each of GIP90, GIP130a, GIP130b, GIP130c, and DOC1 proteins, these polypeptides, or antibodies

thereto, can be used to generally modify aggregation of the GIP90/130 polypeptides and DOC1/DOC1-related proteins. Despite the fact that DOC1 proteins contain SEQ ID NO:20, they do not interact in a two hybrid assay with GPBP (see below), and thus SEQ ID NO:20, while implicated in the interaction of GIP90/130 polypeptides and GPBP, is not sufficient for GPBP interaction.

The polypeptides of the invention also include polypeptides comprising and/or consisting of the amino acid sequence of SEQ ID NO:36, which consists of the first 240 amino acids of the N-terminus of GIP130b, which is not present in DOC1 proteins, and which differs from the corresponding sequence in GIP90, GIP130a, and GIP130c by a single amino acid residue at position 168. This polypeptide includes sequences implicated in (a) the interaction between GPBP and GIP90/130 polypeptides, (b) GIP90/130 polypeptide aggregation, and (c) the transcriptional activity of GIP90/130 polypeptides, and thus the polypeptides, or antibodies derived therefrom, can be used, for example, to modify interactions between GPBP and GIP90/130 polypeptides, to modify GIP90/130 aggregation, and to modulate gene expression.

In a still further embodiment, the isolated GIP 90/130 polypeptide consists of the amino acid sequence of SEQ ID NO:38 which is a unique 384 amino acid polypeptide that is present at the C terminus of GIP130b/c and DOC1-related protein but is not present in GIP90, is not wholly present in DOC1, and includes variations from GIP130a, and thus can be used, for example, to modify GIP130b/c aggregation, and to generate reagents, such as antibodies, to distinguish GIP130b/c and the DOC1-related protein from other members of the GIP90/130 polypeptide family.

As used herein, an "isolated polypeptide" refers to a polypeptide that is substantially free of other proteins, cellular material and culture medium when isolated from cells or produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. Thus, the protein can either be purified from natural sources, chemically synthesized, or recombinant protein can be purified from the recombinant host cells disclosed below.

Synthetic polypeptides, prepared using the well known techniques of solid phase, liquid phase, or peptide condensation techniques, or any combination thereof, can include natural and unnatural amino acids. Amino acids used for peptide synthesis may be standard Boc (Nα-amino protected Nα-t-butyloxycarbonyl) amino acid resin with the standard deprotecting, neutralization, coupling and wash protocols of the original solid phase procedure of Merrifield (1963, J. Am. Chem. Soc. 85:2149-2154),

or the base-labile Nα-amino protected 9-fluorenylmethoxycarbonyl (Fmoc) amino acids first described by Carpino and Han (1972, J. Org. Chem. 37:3403-3409). Both Fmoc and Boc Nα-amino protected amino acids can be obtained from Sigma, Cambridge Research Biochemical, or other chemical companies familiar to those skilled in the art. In addition, the polypeptides can be synthesized with other Nα-protecting groups that are familiar to those skilled in this art.

Solid phase peptide synthesis may be accomplished by techniques familiar to those in the art and provided, for example, in Stewart and Young, 1984, Solid Phase Synthesis, Second Edition, Pierce Chemical Co., Rockford, Ill.; Fields and Noble, 1990, Int. J. Pept. Protein Res. 35:161-214, or using automated synthesizers. The polypeptides of the invention may comprise D-amino acids (which are resistant to L-amino acid-specific proteases in vivo), a combination of D- and L-amino acids, and various "designer" amino acids (e.g., β-methyl amino acids, Cα-methyl amino acids, and Nα-methyl amino acids, etc.) to convey special properties. Synthetic amino acids include ornithine for lysine, fluorophenylalanine for phenylalanine, and norleucine for leucine or isoleucine.

In addition, the polypeptides can have peptidomimetic bonds, such as ester bonds, to prepare peptides with novel properties. For example, a peptide may be generated that incorporates a reduced peptide bond, i.e., R_1-CH_2-NH-R_2, where R_1 and R_2 are amino acid residues or sequences. A reduced peptide bond may be introduced as a dipeptide subunit. Such a polypeptide would be resistant to protease activity, and would possess an extended half-live in vivo.

Alternatively, the proteins are produced by the recombinant host cells disclosed below, and purified using standard techniques. (See for example, *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press.)) The protein can thus be purified from prokaryotic or eukaryotic sources. In various further preferred embodiments, the protein is purified from bacterial, yeast, or mammalian cells.

The protein may comprise additional sequences useful for promoting purification of the protein, such as epitope tags and transport signals. Examples of such epitope tags include, but are not limited to FLAG (Sigma Chemical, St. Louis, MO), myc (9E10) (Invitrogen, Carlsbad, CA), 6-His (Invitrogen; Novagen, Madison, WI), and HA (Boehringer Manheim Biochemicals). Examples of such transport signals include,

but are not limited to, export signals, secretory signals, nuclear localization signals, and plasma membrane localization signals.

In another aspect, the present invention provides antibodies against the GIP90/130 polypeptides disclosed herein. Such antibodies can be used in a manner similar to the polypeptides they recognize in modifying GPBP-GIP90/130 interactions, modifying GIP90/130 aggregation, and/or modifying GIP90/130-mediated transcriptional activity. Furthermore, such antibodies can be used to distinguish between members of the GIP90/130 family, as discussed above.

In one embodiment, the antibodies are directed against an epitope present in a polypeptide of one or more of the amino acid sequences selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:18, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:32, and SEQ ID NO:36. In a further embodiment, the antibodies are directed against an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO: 28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, and SEQ ID NO:38.

Antibodies can be made by well-known methods, such as described in Harlow and Lane, Antibodies; A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., (1988). In one example, pre-immune serum is collected prior to the first immunization. A peptide portion of the amino acid sequence of a GIP90/130 polypeptide, together with an appropriate adjuvant, is injected into an animal in an amount and at intervals sufficient to elicit an immune response. Animals are bled at regular intervals, preferably weekly, to determine antibody titer. The animals may or may not receive booster injections following the initial immunization. At about 7 days after each booster immunization, or about weekly after a single immunization, the animals are bled, the serum collected, and aliquots are stored at about -20° C. Polyclonal antibodies against GIP90/130 polypeptides can then be purified directly by passing serum collected from the animal through a column to which non-antigen-related proteins prepared from the same expression system without GIP90/130 polypeptides bound.

Monoclonal antibodies can be produced by obtaining spleen cells from the animal. (See Kohler and Milstein, Nature 256, 495-497 (1975)). In one example, monoclonal antibodies (mAb) of interest are prepared by immunizing inbred mice with

a GIP90/130 polypeptide, or portion thereof. The mice are immunized by the IP or SC route in an amount and at intervals sufficient to elicit an immune response. The mice receive an initial immunization on day 0 and are rested for about 3 to about 30 weeks. Immunized mice are given one or more booster immunizations of by the intravenous (IV) route. Lymphocytes from antibody positive mice are obtained by removing spleens from immunized mice by standard procedures known in the art. Hybridoma cells are produced by mixing the splenic lymphocytes with an appropriate fusion partner under conditions which will allow the formation of stable hybridomas. The antibody producing cells and fusion partner cells are fused in polyethylene glycol at concentrations from about 30% to about 50%. Fused hybridoma cells are selected by growth in hypoxanthine, thymidine and aminopterin supplemented Dulbecco's Modified Eagles Medium (DMEM) by procedures known in the art. Supernatant fluids are collected from growth positive wells and are screened for antibody production by an immunoassay such as solid phase immunoradioassay. Hybridoma cells from antibody positive wells are cloned by a technique such as the soft agar technique of MacPherson, Soft Agar Techniques, in Tissue Culture Methods and Applications, Kruse and Paterson, Eds., Academic Press, 1973.

To generate such an antibody response, a GIP90/130 polypeptide or portion thereof is typically formulated with a pharmaceutically acceptable carrier for parenteral administration. Such acceptable adjuvants include, but are not limited to, Freund's complete, Freund's incomplete, alum-precipitate, water in oil emulsion containing Corynebacterium parvum and tRNA. The formulation of such compositions, including the concentration of the polypeptide and the selection of the vehicle and other components, is within the skill of the art.

The term antibody as used herein is intended to include antibody fragments thereof which are selectively reactive with GIP90/130 polypeptides. Antibodies can be fragmented using conventional techniques, and the fragments screened for utility in the same manner as described above for whole antibodies. For example, $F(ab')_2$ fragments can be generated by treating antibody with pepsin. The resulting $F(ab')_2$ fragment can be treated to reduce disulfide bridges to produce Fab' fragments.

In another aspect, the present invention provides isolated nucleic acids that encode GIP90/130 polypeptides. In one embodiment, the isolated nucleic acid sequences comprise sequences encoding an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID

NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO: 28, SEQ ID NO:32, and SEQ ID NO:36. In a further embodiment, the isolated nucleic acid sequences consist of sequences encoding an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO: 28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO;34, SEQ ID NO:36, and SEQ ID NO:38.

In another embodiment, the isolated nucleic acids comprise sequences that hybridize under high stringency conditions to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:17, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:31, and SEQ ID NO:35, their complement, or their transcription product. Stringency of hybridization is used herein to refer to conditions under which nucleic acid hybrids are stable. As known to those of skill in the art, the stability of hybrids is reflected in the melting temperature (T_M) of the hybrids. T_M decreases approximately 1-1.5°C with every 1% decrease in sequence homology. In general, the stability of a hybrid is a function of sodium ion concentration and temperature. Typically, the hybridization reaction is performed under conditions of lower stringency, followed by washes of varying, but higher, stringency. Reference to hybridization stringency relates to such washing conditions. Thus, as used herein, high stringency refers to conditions that permit hybridization of those nucleic acid sequences that form stable hybrids in 0.1% SSPE at 65°C. It is understood that these conditions may be duplicated using a variety of buffers and temperatures and that they are not necessarily precise. Denhardt's solution and SSPE (see, e.g., Sambrook, Fritsch, and Maniatis, in: Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press, 1989) are well known to those of skill in the art, as are other suitable hybridization buffers.

In another embodiment, the isolated nucleic acids comprise one or more sequences selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:17, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:31, and SEQ ID NO:35, their complement, or their transcription product. In a further embodiment, the isolated nucleic acid sequences comprise one or more sequences selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID

NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:31, and SEQ ID NO:35, their complement, or their transcription product. In a further embodiment, the isolated nucleic acid sequences consist of one or more sequences selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, and SEQ ID NO:37, their complement, or their transcription product.

As used herein, an "isolated nucleic acid sequence" refers to a nucleic acid sequence that is free of gene sequences which naturally flank the nucleic acid in the genomic DNA of the organism from which the nucleic acid is derived (i.e., genetic sequences that are located adjacent to the gene for the isolated nucleic molecule in the genomic DNA of the organism from which the nucleic acid is derived). An "isolated" GIP90/130 nucleic acid sequence according to the present invention may, however, be linked to other nucleotide sequences that do not normally flank the recited sequence, such as a heterologous promoter sequence, or other vector sequences. It is not necessary for the isolated nucleic acid sequence to be free of other cellular material to be considered "isolated", as a nucleic acid sequence according to the invention may be part of an expression vector that is used to transfect host cells (see below).

In all of these embodiments, the isolated nucleic acid sequence may comprise RNA or DNA, and may be single stranded or double stranded. Such single stranded sequences can comprise the disclosed sequence, its complement, or the transcription product thereof. The isolated sequence may further comprise additional sequences useful for promoting expression and/or purification of the encoded protein, including but not limited to polyA sequences, modified Kozak sequences, and sequences encoding epitope tags, export signals, and secretory signals, nuclear localization signals, and plasma membrane localization signals.

In another embodiment, the present invention provides an expression vector comprising an isolated nucleic acid as described above, operatively linked to a promoter. In a preferred embodiment, the promoter is heterologous (i.e.: is not the naturally occurring GIP90/130 promoter). A promoter and a GIP90/130 nucleic acid sequence are "operatively linked" when the promoter is capable of driving expression of the GIP90/130 DNA into RNA.

As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA into which additional DNA segments may be cloned. Another type of vector is a viral vector, wherein additional DNA segments may be cloned into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors), are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of nucleic acid sequences to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" or simply "expression vectors". In the present invention, the expression of any nucleic acid sequence is directed by operatively linking the promoter sequences of the invention to the nucleic acid sequence to be expressed. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The vector may also contain additional sequences, such as a polylinker for subcloning of additional nucleic acid sequences and a polyadenylation signal to effect proper polyadenylation of the transcript. The nature of the polyadenylation signal is not believed to be crucial to the successful practice of the invention, and any such sequence may be employed, including but not limited to the SV40 and bovine growth hormone poly-A sites. The vector may further include a termination sequence, which can serve to enhance message levels and to minimize read through from the construct into other sequences. Finally, expression vectors typically have selectable markers, often in the form of antibiotic resistance genes, that permit selection of cells that carry these vectors.

In a further embodiment, the present invention provides recombinant host cells in which the expression vectors disclosed herein have been introduced. As used herein, the term "host cell" is intended to refer to a cell into which a nucleic acid of the invention, such as a recombinant expression vector of the invention, has been introduced. Such cells may be prokaryotic or eukaryotic.

The terms "host cell" and "recombinant host cell" are used interchangeably herein. It should be understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

The host cells can be transiently or stably transfected with one or more of the expression vectors of the invention. Such transfection of expression vectors into prokaryotic and eukaryotic cells can be accomplished via any technique known in the art, including but not limited to standard bacterial transformations, calcium phosphate co-precipitation, electroporation, or liposome mediated-, DEAE dextran mediated-, polycationic mediated-, or viral mediated transfection. Alternatively, the host cells can be infected with a recombinant viral vector comprising the GIP90/130 nucleic acid. (See, for example, *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press; *Culture of Animal Cells: A Manual of Basic Technique, 2nd Ed.* (R.I. Freshney. 1987. Liss, Inc. New York, NY).

In a further aspect, the invention provides methods for detecting the presence of the GIP90/130 polypeptides in a protein sample, comprising providing a protein sample to be screened, contacting the protein sample to be screened with an antibody against one or more GIP90/130 polypeptides, and detecting the formation of antibody-GIP90/130 polypeptide complexes. The antibody can be either polyclonal or monoclonal, although monoclonal antibodies are preferred. As used herein, the term "protein sample" refers to any sample that may contain GIP90/130 polypeptides, including but not limited to tissues and portions thereof, tissue sections, intact cells, cell extracts, purified or partially purified protein samples, bodily fluids, and nucleic acid expression libraries. Accordingly, this aspect of the present invention may be used to test for the presence of GIP90/130 polypeptides in these various protein samples by standard techniques including, but not limited to, immunolocalization, immunofluorescence analysis, Western blot analysis, ELISAs, and nucleic acid expression library screening, (See for example, Sambrook et al, 1989.) In one embodiment, the techniques may determine only the presence or absence of GIP90/130 polypeptides. Alternatively, the techniques may be quantitative, and provide information about the relative amount of GIP90/130 polypeptides in the sample. For quantitative purposes, ELISAs are preferred.

Detection of immunocomplex formation between GIP90/130 polypeptides and antibodies or fragments thereof directed against GIP90/130 polypeptides can be accomplished by standard detection techniques. For example, detection of immunocomplexes can be accomplished by using labeled antibodies or secondary antibodies. Such methods, including the choice of label are known to those ordinarily skilled in the art. (Harlow and Lane, Supra). Alternatively, the polyclonal or monoclonal antibodies can be coupled to a detectable substance. The term "coupled" is used to mean that the detectable substance is physically linked to the antibody. Suitable detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase. Examples of suitable prosthetic-group complexes include streptavidin/biotin and avidin/biotin. Examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin. An example of a luminescent material includes luminol. Examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

Such methods of detection are useful for a variety of purposes, including but not limited to detecting an autoimmune condition, identifying cell division arrest or cell death, detecting GIP90/130 interactions with GPBP or other proteins, immunolocalization of GIP90/130 polypeptides in a tissue sample, Western blot analysis, and screening of expression libraries to find related proteins.

In yet another aspect, the invention provides methods for detecting the presence of nucleic acid sequences encoding GIP90/130 polypeptides in a sample comprising providing a nucleic acid sample to be screened, contacting the sample with a nucleic acid probe derived from the isolated nucleic acid sequences of the invention, or fragments thereof, and detecting complex formation.

As used herein, the term "sample" refers to any sample that may contain a GIP90/130 polypeptide-encoding nucleic acid, including but not limited to tissues and portions thereof, tissue sections, intact cells, cell extracts, purified or partially purified nucleic acid samples, DNA libraries, and bodily fluids. Accordingly, this aspect of the present invention may be used to test for the presence of GIP90/130 polypeptide-encoding mRNA or DNA in these various samples by standard techniques including, but not limited to, in situ hybridization, Northern blotting, Southern blotting, DNA library screening, polymerase chain reaction (PCR) or reverse transcription-PCR (RT-PCR).

(See for example, Sambrook et al, 1989.) In one embodiment, the techniques may determine only the presence or absence of the nucleic acid of interest. Alternatively, the techniques may be quantitative, and provide information about the relative amount of the nucleic acid of interest in the sample. For quantitative purposes, quantitative PCR and RT-PCR are preferred. Thus, in one example, RNA is isolated from a sample, and contacted with an oligonucleotide derived from the GIP90/130 polypeptide-encoding nucleic acid sequence, together with reverse transcriptase, under suitable buffer and temperature conditions to produce cDNAs from the GIP90/130 RNA. The cDNA is then subjected to PCR using primer pairs derived from the appropriate nucleic acid sequence disclosed herein. In a preferred embodiment, the primers are designed to detect the presence of the RNA expression product of GIP90/130, and the amount of GIP90/130 gene expression in the sample is compared to the level in a control sample.

For detecting GIP90/130 nucleic acid sequences, standard labeling techniques can be used to label the probe, the nucleic acid of interest, or the complex between the probe and the nucleic acid of interest, including, but not limited to radio-, enzyme-, chemiluminescent-, or avidin or biotin-labeling techniques, all of which are well known in the art. (See, for example, *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), *Gene Expression Technology* (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press, San Diego, CA); *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press, San Diego, CA)).

Such methods of nucleic acid detection are useful for a variety of purposes, including but not limited to detecting an autoimmune condition, identifying cell division arrest or cell death, identifying cells that express GIP90/130 nucleic acid sequences, in situ hybridization for GIP90/130 gene expression, Northern and Southern blot analysis, and DNA library screening.

As discussed above, GIP90/130 polypeptides are likely to be involved in cell signaling pathways that impair cell division or cause cell death, which are thought to be up-regulated during autoimmune pathogenesis and down-regulated in cancer cells to prevent autoimmune attack during tumor growth. Thus, the detection methods disclosed herein can be used to detect cells that are undergoing such cell death-related processes.

Furthermore, the present invention provides method for treating an autoimmune disorder or cancer comprising modifying the expression or activity of GIP90/130 RNA

or GIP90/130 polypeptides, such as by increasing or decreasing their expression or activity. Modifying the expression or activity of GIP90/130 RNA or GIP90/130 polypeptides can be accomplished by using specific inducers or inhibitors of GIP90/130 polypeptide expression or activity, such as GIP90/130 antibodies, polypeptides representing interactive motifs of GIP90/130 such as those disclosed herein, antisense or RNA interference therapy based on the design of antisense oligonucleotides or double stranded RNAs to the GIP90/130 nucleic acid sequences disclosed herein, cell therapy using host cells expressing one or more GIP90/130 polypeptides, or other techniques known in the art. As used herein, "modification of expression or activity" refers to modifying expression or activity of either the RNA or protein product.

For example, knowing that the GIP90/130 gene is a tumor suppressor gene, that aberrantly increased cell death processes are the basis of specific autoimmune pathogenesis (WO 00/50607), and that aggregates of GIP90/130 polypeptides are expressed in a number of human tissues that are common target of autoimmune responses, the administration of GIP90/130 polypeptides or nucleic acids of the invention, particularly those representing essential interactive motifs for GIP90/130 polypeptide aggregation and/or interaction with other cellular components, such as GPBP, would impact pathogenesis and therefore serve as therapeutic agents for autoimmunity. Alternatively, tumor cells express little or no GPBP or GIP90/130, and thus the administration of the GIP90/130 polypeptide or nucleic acid sequences of the invention, particularly the full length GIP90, GIP130a, GIP130b, and/or GIP130c, alone or in combination with GPBP, is expected to provide a therapeutic benefit in patients with cancer.

While not being limited to any specific mechanism of action, it is believed that a therapeutic benefit in cancer patients would be derived by promoting GIP90/130 interactions with other cellular constituents, such as GPBP and/or GIP90/130 aggregation, whereas a therapeutic benefit to autoimmunity patients would be derived by inhibiting these interactions and/or aggregation.

In another aspect, the invention provides methods for modifying GIP90/130 activity comprising contacting cells with an amount effective of one or more of the polypeptides, antibodies, nucleic acids, or pharmaceutical compositions thereof, of the invention to modify GIP90/130 activity. Such cell contacting can be in vitro or in vivo, and "modifying" includes both increasing or decreasing GIP90/130 activity, including transcription-promoting activity.

In another aspect, the invention provides methods for modifying GPBP activity, comprising contacting cells with an amount effective of one or more of the polypeptides, antibodies, nucleic acids, or pharmaceutical compositions thereof, of the invention to modify GPBP activity. Such cell contacting can be in vitro or in vivo, and "modifying" includes both increasing or decreasing GPBP activity. For example, augmented GPBP activity is associated with autoimmunity, and thus the administration of the GIP90/130 polypeptides or antibodies of the invention (or gene therapy by administration of the GIP90/130 nucleic acid sequences or vectors thereof of the invention) would be expected to impact GPBP-GIP90/130 interactions, and to provide a therapeutic benefit in patients with an autoimmune disorder. Alternatively, tumor cells express little or no GPBP, and thus the co-administration of the GIP90/130 polypeptides of the invention, particularly the full length GIP90, GIP130a, GIP130b, and/or GIP130c, in combination with GPBP, would be expected to provide a therapeutic benefit in patients with cancer.

In another aspect, the present invention provides methods for modifying pol κ76 polypeptide activity, comprising contacting cells with an amount effective of one or more of the polypeptides, antibodies, nucleic acids, or pharmaceutical compositions thereof, of the invention to modify pol κ76 activity. Such cell contacting can be in vitro or in vivo, and "modifying" includes both increasing or decreasing pol κ76 activity. For example, augmented pol κ76 activity is associated with autoimmunity (WO 02/46378), and thus the administration of the GIP90/130 polypeptides or antibodies of the invention (or gene therapy by administration of the GIP90/130 nucleic acid sequences or vectors thereof of the invention) would be expected to impact pol κ76-GIP90/130 interactions, and to provide a therapeutic benefit in patients with an autoimmune disorder.

In practicing the therapeutic methods of the invention, the amount or dosage range of the GIP90/130 polypeptides or antibodies thereto generally ranges between about 0.01 μg/kg body weight and about 10 mg/kg body weight, preferably ranging between about 0.10 μg/kg and about 5 mg/kg body weight, and more preferably between about 1 μg/kg and about 5 mg/kg body weight.

In a further aspect, the present invention provides pharmaceutical compositions, comprising an amount effective of the GIP90/130 polypeptides, antibodies thereto, and nucleic acids disclosed herein to carry out one or more of the therapeutic methods of the invention, and a pharmaceutically acceptable carrier. The GIP90/130 polypeptides, or

antibodies thereto, may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc.

For administration, the polypeptides are ordinarily combined with one or more adjuvants appropriate for the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, acacia, gelatin, sodium alginate, polyvinylpyrrolidine, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compounds of this invention may be dissolved in saline, water, polyethylene glycol, propylene glycol, carboxymethyl cellulose colloidal solutions, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art.

The polypeptides or pharmaceutical compositions thereof may be administered by any suitable route, including orally, parentally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. The term parenteral as used herein includes, subcutaneous, intravenous, intra-arterial, intramuscular, intrasternal, intratendinous, intraspinal, intracranial, intrathoracic, infusion techniques or intraperitoneally. In preferred embodiments, the polypeptides are administered intravenously or subcutaneously.

The polypeptides may be made up in a solid form (including granules, powders or suppositories) or in a liquid form (*e.g.*, solutions, suspensions, or emulsions). The polypeptides of the invention may be applied in a variety of solutions. Suitable solutions for use in accordance with the invention are sterile, dissolve sufficient amounts of the polypeptides, and are not harmful for the proposed application.

The present invention may be better understood with reference to the accompanying examples that are intended for purposes of illustration only and should not be construed to limit the scope of the invention, as defined by the claims appended hereto.

Examples

Identification and Characterization of GIP90/130 polypeptides

We performed a yeast two-hybrid screening on several human cDNA libraries searching for GPBP-interactive proteins. The screenings were performed using full length GPBP as bait, cloned in vector pGBT9 to generate the GAL4 binding domain-fusion protein. With the resulting construct we transformed yeast HF7c cells to obtain a stably transfected cell line which was subsequently transformed with the different cDNA libraries we have used: Human Skeletal Muscle (pGAD10 vector), Human Kidney (pGAD10), Human Pancreas (pGAD10), Human Brain (pACT2) and Hela (pGADGH) cDNA libraries (all from Clontech). The transformations were carried out according to the suppiier's instructions and plated on medium deficient in Trp, Leu and His containing 20 mM 3-amino-1,2,4-triazol. Interactions were assessed following the manufacture's recommendations. Specifically β-galactosidase activity was assayed with X-GAL (0.75 mg/ml) for the lift colony assays and with ortho-nitrophenyl β-D galactopyranoside (0.66 mg/ml) for the in-solution determinations.

We isolated an 800 bp cDNA ("I-20 cDNA") encompassing an open reading frame (ORF) which encodes a 265 residue polypeptide, I-20 **(SEQ ID NO:6)**; from a human skeletal muscle library. Part of the ORF coincided with the ORF encoding DOC1 (down-regulated in ovarian cancer 1) (GenBank accession NP_055705) (Mok et al., Gynecol. Oncol. 52(2):247-252 (1994)), a polypeptide whose encoding mRNA is not found in ovarian cancer cell lines, but is abundantly expressed in normal ovarian cell lines. For this reason, the DOC-1 gene is considered to be a tumor suppressor gene.

Using the I-20 cDNA, we probed a multi-tissue Northern blot (Clontech) to determine the level of expression of the I-20 encoding mRNA in normal human tissues and in a number of human cancer cell lines. The membranes were hybridized with ^{32}P-α-dCTP labelled I-20 cDNA **(SEQ ID NO:5)**, and specific mRNAs species were identified by autoradiography. We identified four mRNA species of 9, 4.4, 4 and 3 Kb. The species of 9, 4.4 and 3 Kb were more abundant in skeletal muscle, while the 4 Kb species displayed similar expression in skeletal muscle, pancreas and lung, and higher expression in heart tissue. With the exception of heart, which contained traces of the 9, 4.4 and 3 Kb species, the rest of the tissues tested mainly expressed the 4 Kb mRNA species. As expected from previous studies for DOC1, I-20 cDNA did not hybridize significantly to any mRNA species from the individual human cancer cell lines tested

(MTN human cancer cell line blot from Clontech), thus confirming I-20 as being encoded by a tumor suppressor gene.

Since the I-20 ORF contained no stop codon and extended 5' past the ORF proposed for DOC1, we explored the possibility that in skeletal muscle I-20 represents a partial sequence of a larger protein. By probing the corresponding cDNA library with the I-20 cDNA, we isolated and characterized by nucleotide sequencing four overlapping cDNA clones which in total comprise an ORF encoding a predicted 764-amino acid polypeptide of 90 kDa that was named GIP90 (SEQ ID NO:10), for GPBP interacting protein 90 kDa. The existence of GIP90 mRNA was confirmed by isolating and nucleotide sequencing a continuous PCR fragment derived from the same library containing the proposed overlapping ORF. The more remarkable structural features of GIP90 are the presence of two nuclear localization signals (NLS), one in the N terminal region and another at the C terminal region, and a highly predictable coiled-coil formation through most of its sequence including two leucine zippers.

Using the cDNA nucleotide sequence of GIP90 ("GIP90 cDNA") (SEQ ID NO: 9) we carried out a BLAST search against the human genome and found that GIP90 cDNA matched at chromosome 3 (3q12) (genomic DNA accession numbers NT_030634 for exon I and NT_033050 for the rest of the exons). We determined the exon/intron structure for the GIP90 genomic sequence, which encompass a total of six exons **(Figure 1)**. Exons I-IV of the GIP90 gene contain 5' untranslatable sequence and encode the first 201 residues of an N-terminal segment of 240 residues that is absent in DOC1 and DOC1-related protein (GenBank accession number AAH27860). Exon V encodes the remaining 39 residues not present in DOC proteins as well as the additional 524-residues of GIP90, and exon VI contains 3' untranslatable sequence.

Comparison of the GIP90 cDNA and the GIP90 genomic sequence revealed the existence of an adenine (A) at position 2720 (A^{2720}) in the GIP90 cDNA that was not present in the GIP90 genomic DNA, suggesting that GIP90 cDNA represents either a cDNA artifact, or a native mRNA species that derives from a DNA polymorphism or mRNA editing. Mutational artifacts are generally unique events unlikely to be found in more than one cDNA molecular species. We have identified A^{2720} in at least two different GIP90 cDNA fragments, representing two different reverse transcription events, and PCR on total cDNA from the human muscle library (Clontech) using a forward primer from exon I and a reverse primer from exon VI, and subsequent direct sequencing, revealed that the resulting cDNA exclusively contained A^{2720}. A

homologous nucleotide was also found in a DOC1 encoding sequence, but not in DOC1-related protein encoding sequences. These results indicate that the A^{2720} in the GIP90 cDNA does not represent an artifact.

In order to further analyze the origin of GIP90 cDNA, we studied the expression of GIP90 in two independent human skeletal muscle tissue samples by RT-PCR. We were unable to amplify GIP90 mRNA from these samples. In contrast, we isolated and characterized a continuous cDNA fragment (**SEQ ID NO:11**) representing a related mRNA species that encodes a 130 kDa polypeptide (1135-residues) that we named GIP130a (**SEQ ID NO:12**). GIP130a results from faithful transcription and translation of the GIP90 genomic sequence (ie: no A^{2720}), suggesting that a specific mechanism for mRNA diversification is responsible for the production of GIP90 encoding mRNA from the GIP90 genomic sequence.

To further explore the mRNA diversification mechanism of the DOC1/GIP90/130 family, we compared the nucleotide sequences encoding DOC1/DOC1-related protein, GIP90, and GIP130a. Several nucleotide differences were identified, namely: (1) DOC-1 and DOC1-related mRNA are devoid of exon I-IV; (2) DOC1 mRNA showed nucleotide deletions of 42- and 18-bp in exon V, and both DOC1 and DOC1-related mRNA contain an additional 276-bp at the 3' end of this exon, which corresponds to an intron sequence in GIP90/130a; (3) DOC-1 and DOC1-related mRNAs are both devoid of exon VI.

Therefore, it appeared that the expression of exon VI is associated with expression of GIP90/130a mRNAs, and that DOC-1 and DOC1-related mRNAs are exclusively encoded by an intron-extended exon V. The existence of DOC-1 mRNAs containing exons I-IV was then assessed by PCR of mRNA from human skeletal muscle and from human 293 cells. We obtained two different cDNAs (**SEQ ID NOS: 13 and 15**) both containing exon I-V sequences and DOC-1 exclusive exon V, and diverging with respect to each other in one single nucleotide (A/G) at position 975, which leads to an amino acid change at position 168 (H^{168}/R^{168}). This results in two different 1133-residue long polypeptides (130-kDa) which we named GIP130b (**SEQ ID NO: 14**) and GIP130c (**SEQ ID NO: 16**), respectively. A comparison of the amino acid sequences of GP90/130 polypeptides and the DOC1 polypeptide family is shown in **Figure 3.**

The amino acid sequence of rat filamin A-interacting protein (FILIP) (Genbank accession number BAC00851) and hypothetical human KIAA1275 protein (Genbank accession number BAA86589) are highly homologous (approximately 50%) to the

GIP90/130 and DOC proteins. This suggests that these genes are related and that FILIP, KIAA1275 and GIP90/130 are likely to share biological functions. Therefore, knowing that FILIP impairs cell migration of cortical neurons (Nature Cell Biology 2002 Jul;4(7):495-501), it is plausible to hypothesize that GIP90/130 polypeptides exert their tumor suppressor activity, at least in part, by impairing cell migration.

The above data demonstrate that the DOC-1/GIP90/130 mRNA family results from a complex diversification mechanism operating on the expression of the corresponding gene (GIP90 genomic sequence). Thus, we have found that the presence of R^{168} or H^{168} is the result of a GIP90 genomic sequence polymorphism. The presence of exon V, which is characteristic of GIP90/GIP130a (exon Va), is linked to the expression of exon VI and represents a complex alternative exon splicing in which the alternative use of two 5' splice sites of an intron is coordinated with the splicing of an alternative 3' terminal exon. Thus, when the more upstream 5' splice site is used to yield a shorter exon V (exon Va), the 3' terminal exon (exon VI) is spliced, whereas when using the more downstream 5' splice site resulting in a larger exon V (exon Vb), the 3' terminal exon (exon VI) is not spliced. Regarding A^{2720}, we still are in the process of determining the specific diversification mechanism responsible for its presence. The exon/ intron structure of the gene for the DOC-1/GIP90/130 family is shown in **Figure 1** and a scheme for the more relevant features regarding mRNA and protein structure for the GIP family is presented in **Figure 2**. Finally, similar genetic diversification mechanisms perhaps are responsible for the deletion of C^{2708} in DOC1 and an aberrant alternative splicing within long exons (previously described for other genes) appears to account for the 42- and 18- bp deletions found in DOC1 mRNA.

The presence of R^{168} in GIP90 generates a putative bipartite NLS signal and a consensus for PKA phosphorylation, whereas the presence of A^{2720} causes a frame-shift in the ORF encoding GIP90, which results in the appearance of a second nuclear localization signal and a premature stop codon. The latter removes a total of 386 residues of the C terminal region that is present in GIP130 proteins. These residues appear to conform to a domain with no predictable coiled-coils containing a number of putative O-glycosylation sites **(Figure 2)**.

Characterization of GIP90/130 interactions

Using a yeast two-hybrid system, we found that the four members of the GIP90/130 interact with GPBP, although to a more limited extent than I-20 **(SEQ ID**

NO:6). GIP90 displayed the strongest interaction with GPBP, whereas individual GIP130 proteins interacted similarly with GPBP, although to a lesser extent than GIP90. These data implicate the C-terminal residues of the GIP130 proteins, which are not present in GIP90, and also the C-terminal residues of GIP90 not present in I-20 in a negative modulation of the interaction of GIP90/130 polypeptides with GPBP. Deletion of the N terminal 240-residues of GIP90, GIP130b, and GIP130c resulted in molecular species that do not interact with GPBP, indicating that the N-terminal region contains residues involved in the interaction of GIP90/130 polypeptides with GPBP. All of these findings account for the observation that I-20 (SEQ ID NO: 6), which contains the bulk of this N terminal region (residues 86-240), and does not harbor the inhibitory C terminal regions, displayed the strongest interaction in a two hybrid system with GPBP. The production of additional I-20 deletion mutants and their use in specific two hybrid studies permitted the identification of two specific regions of I-20 that are essential for GPBP interaction as well as the identification of other residues directly involved but not essential for the interaction (**Figure 4**).

GIP90/130 polypeptides self-aggregate and aggregate with each other in a yeast two-hybrid assays, indicating that, similarly to GPBP (WO 00/50607), GIP90/130 polypeptides aggregate to form homo and hetero oligomers. No significant differences were found among GIP90/130 full length polypeptides in their ability to self-aggregate. Deletion of the N-terminal 240-residues from GIP130b/c results in DOC1-related protein, which aggregates more efficiently and does not interact with GPBP. Since the deleted residues contain motifs for I-20 self-aggregation, it is conceivable that the deleted region contains residues that are critical for GIP90/130 aggregation, but not for DOC/DOC1-related protein aggregation, and that GIP90/130 polypeptides and DOC1 polypeptides aggregate in a different manner. Since the N terminal 240 residues also contain essential residues for GIP90/130 polypeptide interactions with GPBP, this further suggests that GPBP interaction negatively modulates GIP90/130 polypeptide aggregation but not DOC aggregation. Consistently, two hybrid assays using I-20 deletion mutants show that essential sequences for GIP90/130 interactions with GPBP and for I-20 aggregation overlap extensively (**Figure 4**), strongly suggesting that GPBP binding to GIP90/130 polypeptides prevents GIP90/130 polypeptide aggregation but not DOC aggregation. Accordingly, we have observed with a yeast three-hybrid system that GPBP expression efficiently impairs both I-20 and GIP90 aggregation, and that I-20 and GIP90 efficiently impair GPBP aggregation.

Deletion mutants were obtained using specific primers and PCR, followed by cloning of the resulting cDNAs in the pGBT9 and pGAD424 vectors. The assays were performed in SFY526 or HF7c Saccharomyces cerevisiae strains, with pGBT9 as GAL4 binding domain vector and pGAD424 as GAL4 activation domain vector, by the lift colony assay procedure. Briefly, the yeast cells were co-transformed with constructs of both binding domain and activation domain vectors, and the co-transformants were selected in medium deficient in both tryptophan and leucine. After five days of incubation at 30° C the colonies were tested for the expression of β-galactosidase with X-Gal substrate (0.75 mg/ml). The intensity of the blue color displayed in the assay informed us about the relative strength of the interactions. When the assays were performed with the HF7c strain, the interactions were assessed by the lift colony assay procedure and by growth in medium deficient in histidine, tryptophan and leucine. For yeast three-hybrid system, we used the pBRIDGE vector, which allows the conditional expression of a third protein apart from the usual GAL4 binding and activation domain-fusion proteins of the two-hybrid system. In this case, the expression of GPBP or I-20 or GIP90 was driven by Met25 promoter, active in absence of methionine. In these experiments, the transformed SFY526 cells were plated in medium deficient in tryptophan, leucine and methionine, and subjected to the colony lift assay after five days at 30°C. In the case of the strain HF7c the colonies grown in the cited plates were streaked on medium with the additional deficiency of histidine.

In an attempt to establish the viability of these molecular interactions in human cells, the interaction between GIP90 and GPBP was assessed in a mammalian two-hybrid system using 293 cells. We used the CLONTECH mammalian two hybrid kit, with vectors pM and pRK5-GAL4BD as GAL4 binding domain vectors and pVP16 as activation domain vector. We transfected 293 cells by the calcium phosphate procedure with the appropriate constructs and reporter vectors and the interactions determined by the CAT ELISA kit (Roche), following the manufacturer's instructions.

Finally, using a yeast two hybrid system, we investigated the interactions between pol κ/pol κ76 and GPBP/GPBPΔ26 and we got no positive results. However, when we challenged interaction between pol κ or pol κ76 and I-20, we obtained positive results with pol κ76 but not with pol κ. The positive interaction of I-20 with pol κ76 suggests that GIP90 is a biological bridge between GPBP and pol κ76 and that the three

proteins are partners in specific strategies which become deregulated during autoimmune pathogenesis.

From all these data, we conclude that: (1) GIP90/130 polypeptides aggregate in a different manner than DOC/DOC1-related polypeptides; (2) GPBP interacts with GIP90/130 polypeptides and this interaction counteracts GIP90/130 polypeptide aggregation; (3) GPBP does not interact with DOC/DOC1-related proteins, and therefore GPBP is not expected to influence DOC/DOC1-related protein aggregation; (4) I-20 contains essential amino acid sequences involved in GPBP interaction with GIP90/130 polypeptides and in GIP90/130 polypeptide aggregation; (5) the C terminal domain of GIP130 species exerts a negative effect on their interactions with GPBP, and (6) GIP90/130 polypeptides contain sequences not present in I-20 that negatively modulate both GIP90/130 polypeptide interaction with GPBP and GIP90/130 polypeptide aggregation.

Further characterization of GIP90/130

Given that GPBP is a protein kinase, we assessed the capacity of GPBP to phosphorylate GIP90 in vitro by using purified yeast recombinant counterparts. GIP90 was cloned in pHIL-D2 vector in frame with the FLAG tag at N-terminal position and with a 6 histidine tail at C-terminal position. It was expressed in the Pichia pastoris expression system (Invitrogen) and purified with an affinity resin (Clontech) making profit of the polyhistidine tail, using an 8 M urea-containing breaking buffer, which was eliminated by dialysis against Tris-buffered saline. The purified protein was incubated with yeast recombinant GPBP in a suitable reaction buffer and labelled for 12 hours at 30° C. The phosphorylation mixtures were analysed by Western blot using FLAG-specific antibodies (Sigma) and autoradiography. Incubation of purified GIP90 and GPBP in the presence of [γ^{32}P] ATP resulted in ^{32}P incorporation into GIP90, thus confirming that GPBP interacts with GIP90 and phosphorylates it.

Remarkable structural features of GIP90/130 proteins are (1) the existence of two nuclear localization sequences (NLS) whose presence appears to be regulated by single nucleotide replacement or addition (see above); and (2) the existence of a large number of predictable coiled-coil motifs including two leucine zippers. Consequently we have assayed the ability of GIP90/130 and DOC1-related protein to induce transcription from a heterologous promoter of a reporter gene. This was accomplished

by fusing either GIP90, GIP130a, GIP130b or DOC1-related protein to the binding domain of GAL4 transcription factor in a high level expression pAS2-1 vector (Clontech) and transforming SFY526 yeast cells carrying a LacZ reporter gene under the control of a promoter with a GAL4 binding site. Transformants were selected in tryptophan-deficient medium at 30°C for five days and colony lift assays performed. The GIP90, GIP130a, and GIP130b fusion polypeptides, but not DOC1-related protein fusion polypeptides, efficiently induced expression of LacZ, as estimated by the appearance of β-galactosidase activity.

We have also expressed GIP90 in bacteria, and have used the corresponding recombinant protein to immunize both rabbits and mice to obtain respectively polyclonal and monoclonal antibodies specific for GIP proteins. GIP90 was cloned in pGEX vector, in frame with glutathione-S-transpherase cDNA. The resulting construct was used to transform DH5α cells and expression of the GST-GIP90 fusion protein was induced with IPTG and further purified on glutathione affinity column. GST-GIP90 purified protein was used to immunize both rabbits and mice in order to obtain respectively polyclonal and monoclonal antibodies. These antibodies were used to identify a native protein in 293 cells displaying the same mobility as recombinant GIP130 which likely represents endogenous GIP130b or GIP130c, since exon VI appears to not be expressed in these cells, as determined by specific RT-PCR approaches. One of the monoclonal antibodies (Mab3) maps in the N terminal 240 residues of GIP90, whereas Mab 8 maps within the next 509 residues (i.e.: between residues 241-750).

By indirect immunofluorescence on COS-7 cells transiently expressing recombinant GIP90 we have identified cells that expressed GIP90 in the nucleus, cells expressing GIP90 in the cytosol, and cells that expressed GIP90 in both the nucleus and the cytosol. When these cells co-expressed recombinant GIP90 and GPBP, double indirect immunofluorescence revealed expression of the two proteins at the cytosol and in some cells GIP90 was also detected in the nucleus. We have not seen GIP90 and GPBP being co-expressed in the nucleus. Finally, using confocal microscopy and NIH3T3 or 293 cells, we have confirmed nuclear localization of GIP90 and cytosolic co-localization GIP90/GPBP. These cells do not express detectable levels of GIP90/130 polypeptides, as no significant fluorescence was detected when non-transfected cells were incubated with anti-GIP antibodies and an appropriate secondary antibody. For immunofluorescence and confocal microscopy studies, GIP90 cDNA was cloned in

pRK5 mammalian expression vector, and this construct was used alone or co-transfected with GPBP cloned in pCDNA3 vector (Invitrogen), using the DEAE-dextran or calcium phosphate procedures. After 24 hours of incubation at 37°C, the cells were washed with phosphate-buffered saline (PBS), fixed with methanol or methanol:acetone, blocked with 3% BSA in PBS and incubated with a pool of mouse anti-GIP90 monoclonal antibodies and rabbit anti-GPBP polyclonal antibodies. FITC-conjugated anti-mouse IgG and TRITC-conjugated anti-rabbit IgG antibodies were respectively used as secondary antibody.

Finally, we have performed immunohistochemistry studies on paraffin embedded human tissues and have found GIP proteins to localize in a number of cells and structures also expressing GPBP. Immunohistochemistry studies were done on human multi-tissue control slides (Biomeda, Dako), using the ABC peroxidase method. GIP proteins are widely expressed in human tissues, but are more abundantly expressed in some locations. A strong staining is found in smooth muscle cells, particularly in those of vessel walls, with a diffuse cytoplasmic pattern. There is intense expression in alveolar septa, with a linear pattern suggestive of being associated to basement membrane locations, along with cytoplasmic staining of the pneumocytes. The kidneys show expression in the epithelial cells of the tubules, mainly in distant ones, and also in mesangial cells and podocytes of the glomerulus. In the pancreas there is staining in the cells of endocrine Langerhans islets. In the adrenal gland, the cortical cells show higher expression than the medullar cells. In the liver, hepatocytes show expression of the GIP90/130, which is higher at the epithelial cells of the biliary ducts. The white matter of the central nervous system shows diffuse staining with a fibrillar pattern, with presence also found in some neuronal bodies. Expression of the GIP90/130 is also evident at the epithelial cells of the prostate, breast, bronchi and intestine, in striated muscle cells of the myocardium, in secretory cells of the pituitary, and in spermatogonium and Leydig cells in the testicle.

The expression of the GIP90/130 is quite similar to that previously described for GPBP (WO 00/50607), with staining in tissues targeted by autoimmune responses, such as the Langerhans islets (type I diabetes), the white matter of the central nervous system (multiple sclerosis), the biliary ducts (primary biliary cirrhosis), the cortex of the adrenal gland (Addison disease), alveolar septa (Goodpasture syndrome), and spermatogonium (male infertility).

The evidence suggests that GIP90/130 is a family of proteins encoded by a tumor suppressor gene, which display transcription factor activity, and which interact and are phosphorylated by GPBP. Given the role of GPBP in autoimmune pathogenesis and in cancer, GIP90/130 represent a potential therapeutic or therapeutic target in these disorders.

We claim:

1. An isolated polypeptide comprising at least 6 amino acids of the amino acid of SEQ ID NO:2.

2. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:2.

3. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:4.

4. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:6.

5. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:8.

6. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:10.

7. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:12.

8. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:14.

9. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:16.

10. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:32.

11. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:36.

12. The isolated polypeptide of claim 1 consisting of at least 6 amino acids of the amino acid sequence of SEQ ID NO:2.

13. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:2.

14. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:4.

15. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:6.

16. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:8.

17. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:10.

18. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:12.

19. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:14.

20. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:16.

21. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:32.

22. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:36.

23. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:34.

24. The isolated polypeptide of claim 23 wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:34.

25. An isolated polypeptide comprising at least 8 amino acids of the amino acid sequence of SEQ ID NO:18.

26. The isolated polypeptide of claim 25 wherein the polypeptide comprises the amino acid sequence of SEQ ID NO:18.

27. The isolated polypeptide of claim 25 wherein the polypeptide consists of at least 8 amino acids of the amino acid sequence of SEQ ID NO:18.

28. The isolated polypeptide of claim 25 wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:18.

29. An isolated polypeptide consisting of at least 8 amino acids of the amino acid of SEQ ID NO:20.

30. The isolated polypeptide of claim 29 wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:20.

31. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:22.

32. The isolated polypeptide of claim 31 wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:22.

33. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:24.

34. The isolated polypeptide of claim 33 wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:24.

35. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:26.

36. The isolated polypeptide of claim 35 wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:26.

37. An isolated polypeptide comprising at least 6 amino acids of the amino acid sequence of SEQ ID NO:28.

38. The isolated polypeptide of claim 37 wherein the polypeptide comprises the amino acid sequence of SEQ ID NO:28.

39. The isolated polypeptide of claim 37 wherein the polypeptide consists of at least 6 amino acids of the amino acid sequence of SEQ ID NO:28.

40. The isolated polypeptide of claim 37 wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:28.

41. An isolated polypeptide consisting of at least 6 amino acids of the amino acid sequence of SEQ ID NO:30.

42. The isolated polypeptide of claim 41 wherein the polypeptide consist of the sequence of SEQ ID NO:30.

43. An isolated polypeptide consisting of the amino acid sequence of SEQ ID NO:38.

44. An antibody directed against a polypeptide comprising an amino acid sequence of one or more of the amino acid sequences selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:32, and SEQ ID NO:36.

45. The antibody of claim 44 wherein the antibody is directed against a polypeptide comprising an amino acid sequence of one or more of the amino acid sequences selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:18, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:32, and SEQ ID NO:36.

46. An isolated nucleic acid sequence comprising a sequence that hybridizes under high stringency conditions to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:17, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:31, and SEQ ID NO:35.

47. The nucleic acid sequence of claim 46, wherein the isolated nucleic acid sequence comprises a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:17, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:31, and SEQ ID NO:35.

48. The isolated nucleic acid sequence of claim 46, wherein the nucleic acid sequence comprises a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:31, and SEQ ID NO:35.

49. The isolated nucleic acid sequence of claim 46, wherein the nucleic acid encodes an amino acid sequence comprising one or more sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:32, and SEQ ID NO:36.

50. An isolated nucleic acid sequence encoding the polypeptide of any one of claims 1-43.

51. A recombinant expression vector comprising the isolated nucleic acid sequence of any one of claims 46-50.

52. A recombinant host cell transfected with the recombinant expression vector of claim 51.

53. A method for detecting a GIP90/130 polypeptide, comprising

a) providing a protein sample to be screened;

b) contacting the protein sample to be screened with the antibody of claim 44 or 45 under conditions that promote antibody-GIP90/130 polypeptide complex formation; and

c) detecting the formation of antibody-polypeptide complexes, wherein the presence of the antibody-GIP90/130 polypeptide complexes indicates the presence of a GIP90/130 polypeptide in the protein sample.

54. The method of claim 53, wherein detecting comprises a method selected from the group consisting of immunolocalization, immunofluorescence analysis, Western blot analysis, ELISAs, and nucleic acid expression library screening.

55. A method for detecting a GIP90/130 encoding nucleic acid sequence in a sample, comprising

a) contacting the sample with a probe comprising a nucleic acid sequence according to any one of claims 33-37 under conditions that promote complex formation between the probe and a GIP90/130 encoding nucleic acid in the sample; and

b) detecting complex formation between the probe and the GIP90/130 encoding nucleic acid in the sample.

56. A method for modifying interactions between GPBP and GIP90/130 polypeptides comprising contacting cells with an amount effective of a polypeptide according to any one of claims 1-43 to modify the interaction between GPBP and GIP.

57. A method for modifying aggregation of GIP90/130 polypeptides comprising contacting cells with an amount effective of a polypeptide according to any one of claims 1-43 to modify the aggregation of GIP90/130 polypeptides.

58. A method for modifying interaction between GPBP and GIP90/130 polypeptides comprising contacting cells with an amount effective of one or more antibodies directed against a GIP90/130 polypeptide to inhibit the interaction between GPBP and GIP.

59. The method of claim 58 wherein the antibody comprises one or more antibodies according to claim 44 or 45.

60. A method for modifying aggregation of GIP90/130 polypeptides comprising contacting cells with an amount effective of one or more antibodies directed against a GIP90/130 polypeptide to modify the aggregation of GIP 90/130 polypeptides.

61. The method of claim 60 wherein the antibody comprises one or more antibodies according to claim 44 or 45.

62. A method for modifying GIP90/130 polypeptide activity comprising contacting cells with an amount effective of a polypeptide according to any one of claims 1-43 to modify GIP90/130 polypeptide activity.

63. A method for modifying GIP90/130 polypeptide activity comprising contacting cells with an amount effective of one or more antibodies directed against a GIP90/130 polypeptide to modify GIP90/130 polypeptide activity.

64. The method of claim 63 wherein the antibody comprises one or more antibodies according to claim 44 or 45.

65. A pharmaceutical composition comprising:

a) an isolated polypeptide according to any one of claims 1-43; and

b) a pharmaceutically acceptable carrier.

66. A pharmaceutical composition comprising:

a) an antibody specific for one or more GIP90/130 polypeptides; and

b) a pharmaceutically acceptable carrier.

67. A pharmaceutical composition comprising:

a) an antibody according to claim 44 or 45; and

b) a pharmaceutically acceptable carrier.

68. A method for treating a patient with an autoimmune disorder, comprising modifying the expression or activity of one or more GIP90/130 polypeptides in the patient with the autoimmune disorder.

69. A method for treating a patient with a tumor, comprising modifying the expression or activity of one or more GIP90/130 polypeptides in the patient with the tumor.

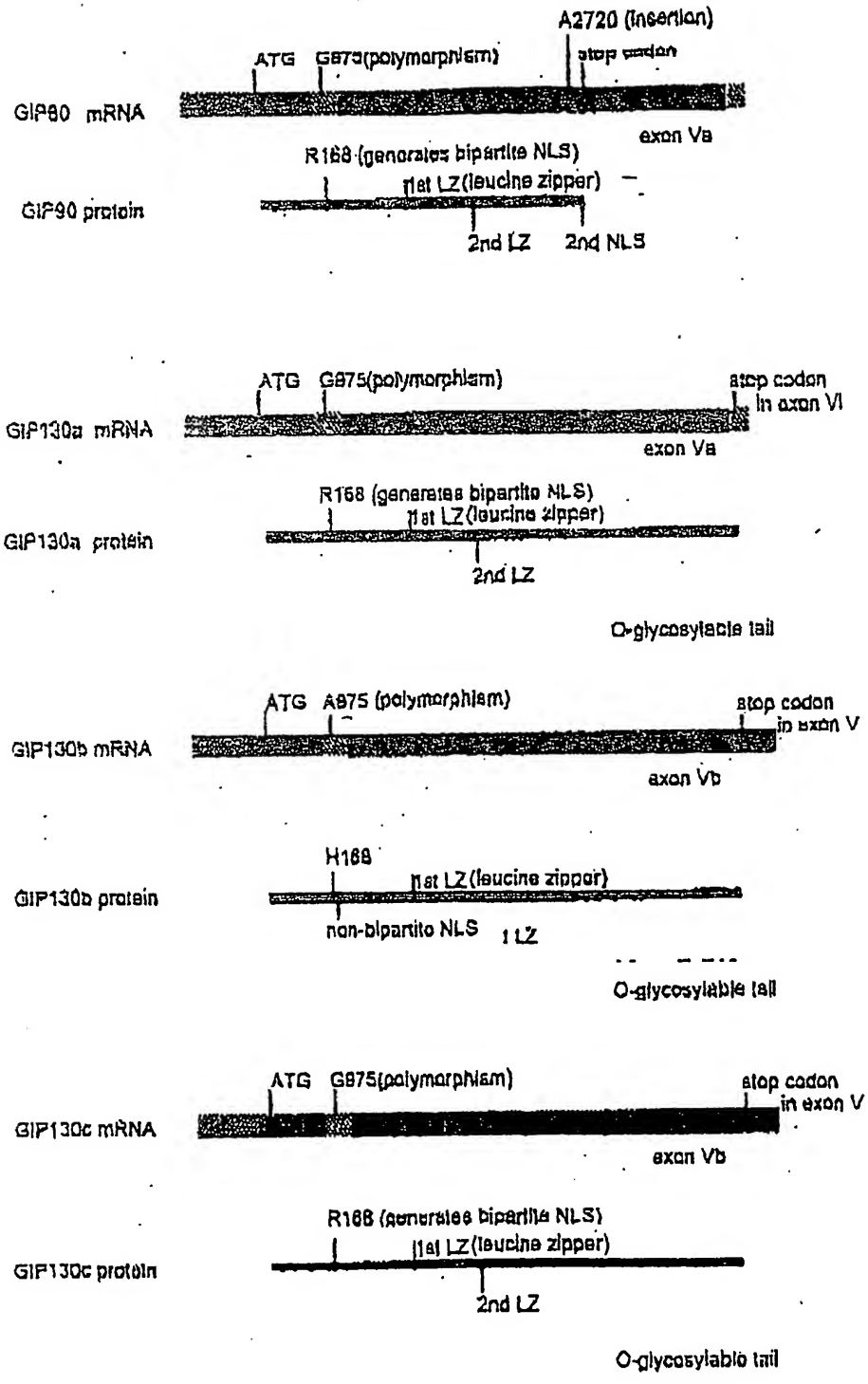
70. A method for modifying interactions between pol k76 and GIP90/130 polypeptides comprising contacting cells with an amount effective of a polypeptide according to any one of claims 1-43 to modify the interaction between pol k76 and GIP.

71. A method for modifying interaction between pol k76 and GIP90/130 polypeptides comprising contacting cells with an amount effective of one or more antibodies directed against a GIP90/130 polypeptide to inhibit the interaction between pol k76 and GIP90/130 polypeptides.

72. The method of claim 71 wherein the antibody comprises one or more antibodies according to claim 44 or 45.

EXON	SIZE	INTRON	SIZE
I	462 bp	I	162 kb
II	262 bp	II	0.9 kb
III	173 bp	III	5.4 kb
IV	179 bp	IV	73.2 kb
V	3056 bp	V	14.8 kb
VI	118 bp		

FIGURE 1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ATG
G875(polymorphism)
stop codon
GIP80 mRNA
exon Va
R168 (generates bipartite NLS)
1st LZ (leucine zipper)
GIP80 protein
2nd LZ
2nd NLS
ATG
G875(polymorphism)
stop codon
in exon VI
GIP130a mRNA
exon Va
R168 (generates bipartite NLS)
1st LZ (leucine zipper)
GIP130a protein
2nd LZ
O-glycosylatable tail
ATG
A875 (polymorphism)
stop codon
in exon V
GIP130b mRNA
exon Vb
H168
1st LZ (leucine zipper)
GIP130b protein
non-bipartite NLS
1 LZ
O-glycosylable tail
ATG
G875(polymorphism)
stop codon
in exon V
GIP130c mRNA
exon Vb
R168 (generates bipartite NLS)
1st LZ (leucine zipper)
GIP130c protein
2nd LZ
O-glycosylable tail

FIGURE 2

FIGURE 3

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GIP90       MRSRGSDTEGSAQKKFPRHTKGHSFQGPKNMKHRQQDKDSPSESDVILPCPKAEKPHSGN
GIP130a     MRSRGSDTEGSAQKKFPRHTKGHSFQGPKNMKHRQQDKDSPSESDVILPCPKAEKPHSGN
GIP130b     MRSRGSDTEGSAQKKFPRHTKGHSFQGPKNMKHRQQDKDSPSESDVILPCPKAEKPHSGN
GIP130c     MRSRGSDTEGSAQKKFPRHTKGHSFQGPKNMKHRQQDKDSPSESDVILPCPKAEKPHSGN
SDOC1       ------------------------------------------------------------
DOC1        ------------------------------------------------------------

GIP90       GHQAEDLSRDDLLFLLSILEGELQARDEVIGILKAEKMDLALLEAQYGFVTPKKVLEALQ
GIP130a     GHQAEDLSRDDLLFLLSILEGELQARDEVIGILKAEKMDLALLEAQYGFVTPKKVLEALQ
GIP130b     GHQAEDLSRDDLLFLLSILEGELQARDEVIGILKAEKMDLALLEAQYGFVTPKKVLEALQ
GIP130c     GHQAEDLSRDDLLFLLSILEGELQARDEVIGILKAEKMDLALLEAQYGFVTPKKVLEALQ
SDOC1       ------------------------------------------------------------
DOC1        ------------------------------------------------------------

GIP90       RDAFQAKSTPWQEDIYEKPMNELDKVVEKHKESYRRILGQLLVAEKSRRQTILELEEEKR
GIP130a     RDAFQAKSTPWQEDIYEKPMNELDKVVEKHKESYRRILGQLLVAEKSRRQTILELEEEKR
GIP130b     RDAFQAKSTPWQEDIYEKPMNELDKVVEKHKESYRRILGQLLVAEKSHRQTILELEEEKR
GIP130c     RDAFQAKSTPWQEDIYEKPMNELDKVVEKHKESYRRILGQLLVAEKSRRQTILELEEEKR
SDOC1       ------------------------------------------------------------
DOC1        ------------------------------------------------------------

GIP90       KHKEYMEKSDEFICLLEQECERLKKLIDQEIKSQEEKEQEKEKRVTTLKEELTKLKSFAL
GIP130a     KHKEYMEKSDEFICLLEQECERLKKLIDQEIKSQEEKEQEKEKRVTTLKEELTKLKSFAL
GIP130b     KHKEYMEKSDEFICLLEQECERLKKLIDQEIKSQEEKEQEKEKRVTTLKEELTKLKSFAL
GIP130c     KHKEYMEKSDEFICLLEQECERLKKLIDQEIKSQEEKEQEKEKRVTTLKEELTKLKSFAL
SDOC1       ------------------------------------------------------------
DOC1        ------------------------------------------------------------

GIP90       MVVDEQQRLTAQLTLQRQKIQELTTNAKETHTKLALAEARVQEEEQKATRLEKELQTQTT
GIP130a     MVVDEQQRLTAQLTLQRQKIQELTTNAKETHTKLALAEARVQEEEQKATRLEKELQTQTT
GIP130b     MVVDEQQRLTAQLTLQRQKIQELTTNAKETHTKLALAEARVQEEEQKATRLEKELQTQTT
GIP130c     MVVDEQQRLTAQLTLQRQKIQELTTNAKETHTKLALAEARVQEEEQKATRLEKELQTQTT
SDOC1       MVVDEQQRLTAQLTLQRQKIQELTTNAKETHTKLALAEARVQEEEQKATRLEKELQTQTT
DOC1        MVVDEQQRLTAQLTLQRQKIQELTTNAKETHTKLALAEARVQEEEQKATRLEKELQTQTT
            ************************************************************

GIP90       KFHQDQDTIMAKLTNEDSQNRQLQQKLAALSRQIDELEETNRSLRKAEEELQDIKEKISK
GIP130a     KFHQDQDTIMAKLTNEDSQNRQLQQKLAALSRQIDELEETNRSLRKAEEELQDIKEKISK
GIP130b     KFHQDQDTIMAKLTNEDSQNRQLQQKLAALSRQIDELEETNRSLRKAEEELQDIKEKISK
GIP130c     KFHQDQDTIMAKLTNEDSQNRQLQQKLAALSRQIDELEETNRSLRKAEEELQDIKEKISK
SDOC1       KFHQDQDTIMAKLTNEDSQNRQLQQKLAALSRQIDELEETNRSLRKAEEELQDIKEKISK
DOC1        KFHQDQDTIMAKLTNEDSQNRQLQQKLAALSRQIDELEETNRSLRKAEEELQDIKEKISK
            ************************************************************

GIP90       GEYGNAGIMAEVEELRKRVLDMEGKDEELIKMEEQCRDLNKRLERETLQSKDFKLEVEKL
GIP130a     GEYGNAGIMAEVEELRKRVLDMEGKDEELIKMEEQCRDLNKRLERETLQSKDFKLEVEKL
GIP130b     GEYGNAGIMAEVEELRKRVLDMEGKDEELIKMEEQCRDLNKRLERETLQSKDFKLEVEKL
GIP130c     GEYGNAGIMAEVEELRKRVLDMEGKDEELIKMEEQCRDLNKRLERETLQSKDFKLEVEKL
SDOC1       GEYGNAGIMAEVEELRKRVLDMEGKDEELIKMEEQCRDLNKRLERETLQSKDFKLEVEKL
DOC1        GEYGNAGIMAEVEEL--------------IKMEEQCRDLNKRLERETLQSKDFKLEVEKL
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GIP90       SKRIMALEKLEDAFNKSKQECYSLKCNLEKERMTTKQLSQELESLKVRIKELEAIESRLE
GIP130a     SKRIMALEKLEDAFNKSKQECYSLKCNLEKERMTTKQLSQELESLKVRIKELEAIESRLE
GIP130b     SKRIMALEKLEDAFNKSKQECYSLKCNLEKERMTTKQLSQELESLKVRIKELEAIESRLE
GIP130c     SKRIMALEKLEDAFNKSKQECYSLKCNLEKERMTTKQLSQELESLKVRIKELEAIESRLE
SDOC1       SKRIMALEKLEDAFNKSKQECYSLKCNLEKERMTTKQLSQELESLKVRIKELEAIESRLE
DOC1        SKRIMALEKLEDAFNKSKQECYSLKCNLEKERMTTKQLSQELESLKVRIKELEAIESRLE
            ************************************************************

GIP90       KTEFTLKEDLTKLKTLTVMFVDERKTMSEKLKKTEDKLQAASSQLQVEQNKVTTVTEKLI
GIP130a     KTEFTLKEDLTKLKTLTVMFVDERKTMSEKLKKTEDKLQAASSQLQVEQNKVTTVTEKLI
GIP130b     KTEFTLKEDLTKLKTLTVMFVDERKTMSEKLKKTEDKLQAASSQLQVEQNKVTTVTEKLI
GIP130c     KTEFTLKEDLTKLKTLTVMFVDERKTMSEKLKKTEDKLQAASSQLQVEQNKVTTVTEKLI
SDOC1       KTEFTLKEDLTKLKTLTVMFVDERKTMSEKLKKTEDKLQAASSQLQVEQNKVTTVTEKLI
DOC1        KTEFTLKEDLTKLKTLTVMFVDERKTMSEKLKKTEDKLQAASSQLQVEQNKVTTVTEKLI
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GIP90       EETKRALKSKTDVEEKMYSVTKERDDLKNKLKAEEEKGNDLLSRVNMLKNRLQSLEAIEK
GIP130a     EETKRALKSKTDVEEKMYSVTKERDDLKNKLKAEEEKGNDLLSRVNMLKNRLQSLEAIEK
GIP130b     EETKRALKSKTDVEEKMYSVTKERDDLKNKLKAEEEKGNDLLSRVNMLKNRLQSLEAIEK
GIP130c     EETKRALKSKTDVEEKMYSVTKERDDLKNKLKAEEEKGNDLLSRVNMLKNRLQSLEAIEK
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DOC1        EETKRALKSKTDVEEKMYSVTKERDDLKNKLKAEEEKGNDLLSRVNMLKNRLQSLEAIEK
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GIP90       DFLKNKLNQDSGKSTTALHQENNKIKELSQEVERLKLKLKDMKAIEDDLMKTEDEYETLE
GIP130a     DFLKNKLNQDSGKSTTALHQENNKIKELSQEVERLKLKLKDMKAIEDDLMKTEDEYETLE
GIP130b     DFLKNKLNQDSGKSTTALHQENNKIKELSQEVERLKLKLKDMKAIEDDLMKTEDEYETLE
GIP130c     DFLKNKLNQDSGKSTTALHQENNKIKELSQEVERLKLKLKDMKAIEDDLMKTEDEYETLE
SDOC1       DFLKNKLNQDSGKSTTALHQENNKIKELSQEVERLKLKLKDMKAIEDDLMKTEDEYETLE
DOC1        DFLKNKLNQDSGKSTTALHQENNKIKELSQEVERLKLKLKDMKAIEDDLMKTEDEYETLE
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GIP90       RRYANERDKAQFLSKELEHVKMELAKYKLAEKTETSHEQWLFKRLQEEEAKSGHLSREVD
GIP130a     RRYANERDKAQFLSKELEHVKMELAKYKLAEKTETSHEQWLFKRLQEEEAKSGHLSREVD
GIP130b     RRYANERDKAQFLSKELEHVKMELAKYKLAEKTETSHEQWLFKRLQEEEAKSGHLSREVD
GIP130c     RRYANERDKAQFLSKELEHVKMELAKYKLAEKTETSHEQWLFKRLQEEEAKSGHLSREVD
SDOC1       RRYANERDKAQFLSKELEHVKMELAKYKLAEKTETSHEQWLFKRLQEEEAKSGHLSREVD
DOC1        RRYANERDKAQFLSKELEHVKMELAKYKLAEKTETSHEQWLFKRLQEEEAKSGHLSREVD
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GIP90       ALKEKIHEYMATEDLICHLQGDHSVLQKKTKSTRKQEQRFRKRD----------------
GIP130a     ALKEKIHEYMATEDLICHLQGDHSVLQKKLNQQENRNRDLGREIENLTKELERYRHFSKS
GIP130b     ALKEKIHEYMATEDLICHLQGDHSVLQKKLNQQENRNRDLGREIENLTKELERYRHFSKS
GIP130c     ALKEKIHEYMATEDLICHLQGDHSVLQKKLNQQENRNRDLGREIENLTKELERYRHFSKS
SDOC1       ALKEKIHEYMATEDLICHLQGDHSVLQKKLNQQENRNRDLGREIENLTKELERYRHFSKS
DOC1        ALKEKIHEYMATEDLICHLQGDHSVCKKKLNQQENRNRDLGREIENLTKELERYRHFSKS
            ************************** :** :. .          :      :*:*: .

GIP90       ------------------------------------------------------------
GIP130a     LRPSLNGRRISDPQVFSKEVQTEAVDNEPPDYKSLIPLERAVINGQLYEESENQDEDPND
GIP130b     LRPSLNGRRISDPQVFSKEVQTEAVDNEPPDYKSLIPLERAVINGQLYEESENQDEDPND
GIP130c     LRPSLNGRRISDPQVFSKEVQTEAVDNEPPDYKSLIPLERAVINGQLYEESENQDEDPND
SDOC1       LRPSLNGRRISDPQVFSKEVQTEAVDNEPPDYKSLIPLERAVINGQLYEESENQDEDPND
DOC1        LRPSLNGRRISDPQVFSKEVQTEAVDNEPPDYKSLIPLERAVINGQLYEESENQDEDPND
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GIP90       ------------------------------------------------------------
GIP130a     EGSVLSFKCSQSTPCPVNRKLWIPWMKSKEGHLQNGKMQTKPNANFVQPGDLVLSHTPGQ
GIP130b     EGSVLSFKCSQSTPCPVNRKLWIPWMKSKEGHLQNGKMQTKPNANFVQPGDLVLSHTPGQ
GIP130c     EGSVLSFKCSQSTPCPVNRKLWIPWMKSKEGHLQNGKMQTKPNANFVQPGDLVLSHTPGQ
SDOC1       EGSVLSFKCSQSTPCPVNRKLWIPWMKSKEGHLQNGKMQTKPNANFVQPGDLVLSHTPGQ
DOC1        EGSVLSFKCSQSTPCPVNRKLWIPWMKSKEGHLQNGKMQTKPNANFVQPGDLVLSHTPGQ

GIP90       ------------------------------------------------------------
GIP130a     PLHIKVTPDHVQNTATLEITSPTTESPHSYTSTAVIPNCGTPKQRITILQNASITPVKSK
GIP130b     PLHIKVTPDHVQNTATLEITSPTTESPHSYTSTAVIPNCGTPKQRITILQNASITPVKSX
GIP130c     PLHIKVTPDHVQNTATLEITSPTTESPHSYTSTAVIPNCGTPKQRITILQNASITPVKSK
SDOC1       PLHIKVTPDHVQNTATLEITSPTTESPHSYTSTAVIPNCGTPKQRITILQNASITPVKSK
DOC1        PLHIKVTPDHVQNTATLEITSPTTESPHSYTSTAVIPNCGTPKQRITILQNASITPVKSK

GIP90       ------------------------------------------------------------
GIP130a     TSTEDLMNLEQGMSPITMATFARAQTPESCGSLTPERTMSPIQVLAVTGSASSPEQGRSP
GIP130b     TSTEDLMNLEQGMSPITMATFARAQTPESCGSLTPERTMSPIQVLAVTGSASSPEQGRSP
GIP130c     TSTEDLMNLEQGMSPITMATFARAQTPESCGSLTPERTMSPIQVLAVTGSASSPEQGRSP
SDOC1       TSTEDLMNLEQGMSPITMATFARAQTPESCGSLTPERTMSPIQVLAVTGSASSPEQGRSP
DOC1        TSTEDLMNLEQGMSPITMATFARAQTPESCGSLTPERTMSLFRFWL--------------

GIP90       ------------------------------------------------------------
GIP130a     EPTEISAKHAIFRVSPDRQSSWQFQRSNSNSSSVITTEDNKIHIHLGSPYMQAVASPVRP
GIP130b     EPTEISAKHAIFRVSPDRQSSWQFQRSNSNSSSVITTEDNKIHIHLGSPYMQAVASPVRP
GIP130c     EPTEISAKHAIFRVSPDRQSSWQFQRSNSNSSSVITTEDNKIHIHLGSPYMQAVASPVRP
SDOC1       EPTEISAKHAIFRVSPDRQSSWQFQRSNSNSSSVITTEDNKIHIHLGSPYMQAVASPVRP
DOC1        ------------------------------------------------------------

GIP90       ------------------------------------------------------
GIP130a     ASPSAPLQDNRTQGLINGALNKTTNKVTSSITITPTATPLPRQSQITVEPLLLPH
GIP130b     ASPSAPLQDNRTQGLINGALNKTTNKVTSSITITPTATPLPRQSQITVSNIYN--
GIP130c     ASPSAPLQDNRTQXLINGALNKTTNKVTSSITITPTATPLPRQSQITVSNIYN--
SDOC1       ASPSAPLQDNRTQGLINGALNKTTNKVTSSITITPTATPLPRQSQITVSNIYN--
DOC1        ------------------------------------------------------
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FIGURE 4

RDEVIGILKAEKMDLALLEAQYGFVTPKKVLEALQRDAFQAKSTPWQEDIYEKPMNEld

kvvekhkeSYRRILGQLLVAEKSRRQTILELEEEKRKHKEYMEKSDEFICLLEQECERL

KKLIDQEIKSQEEKEQEKEKRVTTLKEELTKLKSFALMVVDEQQRLTAQLTLQRQKIQE

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QLQQKLAALSRQIDELEETNRSLRKAEEE

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cca aga cat act aaa ggc cac agt ttc caa ggg cct aaa aac atg aag      96
Pro Arg His Thr Lys Gly His Ser Phe Gln Gly Pro Lys Asn Met Lys
            20                  25                  30

cat aga cag caa gac aaa gac tcc ccc agt gag tcg gat gta ata ctt     144
His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val Ile Leu
        35                  40                  45

ccg tgt ccc aag gca gag aag cca cac agt ggt aat ggc cac caa gca     192
Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His Gln Ala
    50                  55                  60

gaa gac ctc tca aga gat gac ctg tta ttt ctc ctc agc att ctg gag     240
Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile Leu Glu
65                  70                  75                  80

gga gaa ctg cag gct cga gat gag gtc ata ggc att tta aag gct gaa     288
Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu
                85                  90                  95

aaa atg gac ctg gct ttg ctg gaa gct cag tat ggg ttt gtc act cca     336
Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro
            100                 105                 110

aaa aag gtg tta gag gct ctc cag aga gat gct ttt caa gcg aaa tct     384
Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser
        115                 120                 125

acc cct tgg cag gag gac atc tat gag aaa cca atg aat gag ttg gac     432
Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp
    130                 135                 140

aaa gtt gtg gaa aaa cat aaa gaa tct tac aga cga atc ctg gga cag     480
Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln
145                 150                 155                 160

ctt tta gtg gca gaa aaa tcc cgt agg caa acc ata ttg gag ttg gag     528
Leu Leu Val Ala Glu Lys Ser Arg Arg Gln Thr Ile Leu Glu Leu Glu
                165                 170                 175

gaa gaa aag aga aaa cat aaa gaa tac atg gag aag agt gat gaa ttc     576
Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe
            180                 185                 190

ata tgc cta cta gaa cag gaa tgt gaa aga tta aag aag cta att gat     624
Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp
        195                 200                 205

caa gaa atc aag tct cag gag gag aag gag caa gaa aag gag aaa agg     672
Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg
    210                 215                 220

gtc acc acc ctg aaa gag gag ctg acc aag ctg aag tct ttt gct ttg     720
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Pro Arg His Thr Lys Gly His Ser Phe Gln Gly Pro Lys Asn Met Lys
20 25 30

His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val Ile Leu
35 40 45

Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His Gln Ala
50 55 60

Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile Leu Glu
65 70 75 80

Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu
85 90 95

Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro
100 105 110

Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser
115 120 125

Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp
130 135 140

Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln
145 150 155 160

Leu Leu Val Ala Glu Lys Ser Arg Arg Gln Thr Ile Leu Glu Leu Glu
165 170 175

Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe
180 185 190

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Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp
        195                 200                 205

Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg
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Val Thr Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser Phe Ala Leu
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Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu Lys Met Asp Leu Ala
1               5                   10                  15

ttg ctg gaa gct cag tat ggg ttt gtc act cca aaa aag gtg tta gag       96
Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro Lys Lys Val Leu Glu
            20                  25                  30

gct ctc cag aga gat gct ttt caa gcg aaa tct acc cct tgg cag gag      144
Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser Thr Pro Trp Gln Glu
        35                  40                  45

gac atc tat gag aaa cca atg aat gag ttg gac aaa gtt gtg gaa aaa      192
Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp Lys Val Val Glu Lys
    50                  55                  60

cat aaa gaa tct tac aga cga atc ctg gga cag ctt tta gtg gca gaa      240
His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln Leu Leu Val Ala Glu
65                  70                  75                  80

aaa tcc cgt agg caa acc ata ttg gag ttg gag gaa gaa aag aga aaa      288
Lys Ser Arg Arg Gln Thr Ile Leu Glu Leu Glu Glu Glu Lys Arg Lys
                85                  90                  95

cat aaa gaa tac atg gag aag agt gat gaa ttc ata tgc cta cta gaa      336
His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe Ile Cys Leu Leu Glu
            100                 105                 110

cag gaa tgt gaa aga tta aag aag cta att gat caa gaa atc aag tct      384
Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp Gln Glu Ile Lys Ser
        115                 120                 125
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cag gag gag aag gag caa gaa aag gag aaa agg gtc acc acc ctg aaa      432
Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg Val Thr Thr Leu Lys
    130                 135                 140

gag gag ctg acc aag ctg aag tct ttt gct ttg atg gtg gtg gat gaa      480
Glu Glu Leu Thr Lys Leu Lys Ser Phe Ala Leu Met Val Val Asp Glu
145                 150                 155                 160

cag caa agg ctg acg gca cag ctc acc ctt caa aga cag aaa atc caa      528
Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln Arg Gln Lys Ile Gln
                165                 170                 175

gag ctg acc aca aat gca aag gaa aca cat acc aaa cta gcc ctt gct      576
Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr Lys Leu Ala Leu Ala
            180                 185                 190

gaa gcc aga gtt cag gag gaa gag cag aag gca acc aga cta gag aag      624
Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala Thr Arg Leu Glu Lys
        195                 200                 205

gaa ctg caa acg cag acc aca aag ttt cac caa gac caa gac aca att      672
Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln Asp Gln Asp Thr Ile
    210                 215                 220

atg gcg aag ctc acc aat gag gac agt caa aat cgc cag ctt caa caa      720
Met Ala Lys Leu Thr Asn Glu Asp Ser Gln Asn Arg Gln Leu Gln Gln
225                 230                 235                 240

aag ctg gca gca ctc agc cgg cag att gat gag tta gaa gag aca aac      768
Lys Leu Ala Ala Leu Ser Arg Gln Ile Asp Glu Leu Glu Glu Thr Asn
                245                 250                 255

agg tct tta cga aaa gca gaa gag gag                                  795
Arg Ser Leu Arg Lys Ala Glu Glu Glu
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            20                  25                  30

Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser Thr Pro Trp Gln Glu
        35                  40                  45

Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp Lys Val Val Glu Lys
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His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln Leu Leu Val Ala Glu
65 70 75 80

Lys Ser Arg Arg Gln Thr Ile Leu Glu Leu Glu Glu Glu Lys Arg Lys
85 90 95

His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe Ile Cys Leu Leu Glu
100 105 110

Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp Gln Glu Ile Lys Ser
115 120 125

Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg Val Thr Thr Leu Lys
130 135 140

Glu Glu Leu Thr Lys Leu Lys Ser Phe Ala Leu Met Val Val Asp Glu
145 150 155 160

Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln Arg Gln Lys Ile Gln
165 170 175

Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr Lys Leu Ala Leu Ala
180 185 190

Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala Thr Arg Leu Glu Lys
195 200 205

Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln Asp Gln Asp Thr Ile
210 215 220

Met Ala Lys Leu Thr Asn Glu Asp Ser Gln Asn Arg Gln Leu Gln Gln
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cca aga cat act aaa ggc cac agt ttc caa ggg cct aaa aac atg aag      96
Pro Arg His Thr Lys Gly His Ser Phe Gln Gly Pro Lys Asn Met Lys
            20                  25                  30

cat aga cag caa gac aaa gac tcc ccc agt gag tcg gat gta ata ctt     144
His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val Ile Leu
        35                  40                  45

ccg tgt ccc aag gca gag aag cca cac agt ggt aat ggc cac caa gca     192
Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His Gln Ala
    50                  55                  60

gaa gac ctc tca aga gat gac ctg tta ttt ctc ctc agc att ctg gag     240
Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile Leu Glu
65                  70                  75                  80

gga gaa ctg cag gct cga gat gag gtc ata ggc att tta aag gct gaa     288
Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu
            85                  90                  95

aaa atg gac ctg gct ttg ctg gaa gct cag tat ggg ttt gtc act cca     336
Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro
            100                 105                 110

aaa aag gtg tta gag gct ctc cag aga gat gct ttt caa gcg aaa tct     384
Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser
        115                 120                 125

acc cct tgg cag gag gac atc tat gag aaa cca atg aat gag ttg gac     432
Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp
    130                 135                 140

aaa gtt gtg gaa aaa cat aaa gaa tct tac aga cga atc ctg gga cag     480
Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln
145                 150                 155                 160

ctt tta gtg gca gaa aaa tcc cgt agg caa acc ata ttg gag ttg gag     528
Leu Leu Val Ala Glu Lys Ser Arg Arg Gln Thr Ile Leu Glu Leu Glu
                165                 170                 175

gaa gaa aag aga aaa cat aaa gaa tac atg gag aag agt gat gaa ttc     576
Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe
            180                 185                 190
```

```
ata tgc cta cta gaa cag gaa tgt gaa aga tta aag aag cta att gat      624
Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp
        195                 200                 205

caa gaa atc aag tct cag gag gag aag gag caa gaa aag gag aaa agg      672
Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg
    210                 215                 220

gtc acc acc ctg aaa gag gag ctg acc aag ctg aag tct ttt gct ttg      720
Val Thr Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser Phe Ala Leu
225                 230                 235                 240

atg gtg gtg gat gaa cag caa agg ctg acg gca cag ctc acc ctt caa      768
Met Val Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln
                245                 250                 255

aga cag aaa atc caa gag ctg acc aca aat gca aag gaa aca cat acc      816
Arg Gln Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr
            260                 265                 270

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        275                 280                 285

acc aga cta gag aag gaa ctg caa acg cag acc aca aag ttt cac caa      912
Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln
    290                 295                 300

gac caa gac aca att atg gcg aag ctc acc aat gag gac agt caa aat      960
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305                 310                 315                 320

cgc cag ctt caa caa aag ctg gca gca ctc agc cgg cag att gat gag     1008
Arg Gln Leu Gln Gln Lys Leu Ala Ala Leu Ser Arg Gln Ile Asp Glu
                325                 330                 335

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            20                  25                  30

His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val Ile Leu
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Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His Gln Ala
50 55 60

Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile Leu Glu
65 70 75 80

Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu
85 90 95

Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro
100 105 110

Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser
115 120 125

Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp
130 135 140

Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln
145 150 155 160

Leu Leu Val Ala Glu Lys Ser Arg Arg Gln Thr Ile Leu Glu Leu Glu
165 170 175

Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe
180 185 190

Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp
195 200 205

Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg
210 215 220

Val Thr Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser Phe Ala Leu
225 230 235 240

Met Val Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln
245 250 255

Arg Gln Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr
260 265 270

Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala
275 280 285

Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln
290 295 300

Asp Gln Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp Ser Gln Asn
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cctttcttcc acagagactg gcaagctgtg gggtaagagt tttggtaagg ctgcctgtct 180

tcagagcatg aaggacactg cccggagagg gaagagggca atatttagtg tttgggccta 240

cttgttgttg ggctccccac tgcctctcct ttgcagagct atcactggcc cctggttgca 300

aactctcggt ggctttcaag cctacaaaac aaaaactgag agggtgtcca aaaagagaag 360

aagaaaacgt tgttgttggt cctggattcc actgttggat tttggtgggg atgagaagaa 420

ggaattacca ggtgtgatca acacctgcac ggtacctgca cggctttaaa ga atg cgt 478
Met Arg
1

tcc aga ggc agt gat acc gag ggc tca gcc caa aag aaa ttt cca aga 526

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Ser Arg Gly Ser Asp Thr Glu Gly Ser Ala Gln Lys Lys Phe Pro Arg
        5                  10                  15

cat act aaa ggc cac agt ttc caa ggg cct aaa aac atg aag cat aga      574
His Thr Lys Gly His Ser Phe Gln Gly Pro Lys Asn Met Lys His Arg
    20                  25                  30

cag caa gac aaa gac tcc ccc agt gag tcg gat gta ata ctt ccg tgt      622
Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val Ile Leu Pro Cys
35                  40                  45                  50

ccc aag gca gag aag cca cac agt ggt aat ggc cac caa gca gaa gac      670
Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His Gln Ala Glu Asp
                55                  60                  65

ctc tca aga gat gac ctg tta ttt ctc ctc agc att ctg gag gga gaa      718
Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile Leu Glu Gly Glu
            70                  75                  80

ctg cag gct cga gat gag gtc ata ggc att tta aag gct gaa aaa atg      766
Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu Lys Met
        85                  90                  95

gac ctg gct ttg ctg gaa gct cag tat ggg ttt gtc act cca aaa aag      814
Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro Lys Lys
    100                 105                 110

gtg tta gag gct ctc cag aga gat gct ttt caa gcg aaa tct acc cct      862
Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser Thr Pro
115                 120                 125                 130

tgg cag gag gac atc tat gag aaa cca atg aat gag ttg gac aaa gtt      910
Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp Lys Val
                135                 140                 145

gtg gaa aaa cat aaa gaa tct tac aga cga atc ctg gga cag ctt tta      958
Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln Leu Leu
            150                 155                 160

gtg gca gaa aaa tcc cgt agg caa acc ata ttg gag ttg gag gaa gaa     1006
Val Ala Glu Lys Ser Arg Arg Gln Thr Ile Leu Glu Leu Glu Glu Glu
        165                 170                 175

aag aga aaa cat aaa gaa tac atg gag aag agt gat gaa ttc ata tgc     1054
Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe Ile Cys
    180                 185                 190

cta cta gaa cag gaa tgt gaa aga tta aag aag cta att gat caa gaa     1102
Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp Gln Glu
195                 200                 205                 210

atc aag tct cag gag gag aag gag caa gaa aag gag aaa agg gtc acc     1150
Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg Val Thr
                215                 220                 225

acc ctg aaa gag gag ctg acc aag ctg aag tct ttt gct ttg atg gtg     1198
Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser Phe Ala Leu Met Val
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            230                 235                 240

gtg gat gaa cag caa agg ctg acg gca cag ctc acc ctt caa aga cag     1246
Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln Arg Gln
        245                 250                 255

aaa atc caa gag ctg acc aca aat gca aag gaa aca cat acc aaa cta     1294
Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr Lys Leu
    260                 265                 270

gcc ctt gct gaa gcc aga gtt cag gag gaa gag cag aag gca acc aga     1342
Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala Thr Arg
275                 280                 285                 290

cta gag aag gaa ctg caa acg cag acc aca aag ttt cac caa gac caa     1390
Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln Asp Gln
                295                 300                 305

gac aca att atg gcg aag ctc acc aat gag gac agt caa aat cgc cag     1438
Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp Ser Gln Asn Arg Gln
            310                 315                 320

ctt caa caa aag ctg gca gca ctc agc cgg cag att gat gag tta gaa     1486
Leu Gln Gln Lys Leu Ala Ala Leu Ser Arg Gln Ile Asp Glu Leu Glu
        325                 330                 335

gag aca aac agg tct tta cga aaa gca gaa gag gag ctg caa gat ata     1534
Glu Thr Asn Arg Ser Leu Arg Lys Ala Glu Glu Glu Leu Gln Asp Ile
    340                 345                 350

aaa gaa aaa atc agt aag gga gaa tat gga aac gct ggt atc atg gct     1582
Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn Ala Gly Ile Met Ala
355                 360                 365                 370

gaa gtg gaa gag ctc agg aaa cgt gtg cta gat atg gaa ggg aaa gat     1630
Glu Val Glu Glu Leu Arg Lys Arg Val Leu Asp Met Glu Gly Lys Asp
                375                 380                 385

gaa gag ctc ata aaa atg gag gag cag tgc aga gat ctc aat aag agg     1678
Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp Leu Asn Lys Arg
            390                 395                 400

ctt gaa agg gag acg tta cag agt aaa gac ttt aaa cta gag gtt gaa     1726
Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys Leu Glu Val Glu
        405                 410                 415

aaa ctc agt aaa aga att atg gct ctg gaa aag tta gaa gac gct ttc     1774
Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu Glu Asp Ala Phe
    420                 425                 430

aac aaa agc aaa caa gaa tgc tac tct ctg aaa tgc aat tta gaa aaa     1822
Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys Asn Leu Glu Lys
435                 440                 445                 450

gaa agg atg acc aca aag cag ttg tct caa gaa ctg gag agt tta aaa     1870
Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu Glu Ser Leu Lys
                455                 460                 465
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gta agg atc aaa gag cta gaa gcc att gaa agt cgg cta gaa aag aca     1918
Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg Leu Glu Lys Thr
            470                 475                 480

gaa ttc act cta aaa gag gat tta act aaa ctg aaa aca tta act gtg     1966
Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys Thr Leu Thr Val
        485                 490                 495

atg ttt gta gat gaa cgg aaa aca atg agt gaa aaa tta aag aaa act     2014
Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys Leu Lys Lys Thr
    500                 505                 510

gaa gat aaa tta caa gct gct tct tct cag ctt caa gtg gag caa aat     2062
Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln Val Glu Gln Asn
515                 520                 525                 530

aaa gta aca aca gtt act gag aag tta att gag gaa act aaa agg gcg     2110
Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu Thr Lys Arg Ala
                535                 540                 545

ctc aag tcc aaa acc gat gta gaa gaa aag atg tac agc gta acc aag     2158
Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr Ser Val Thr Lys
            550                 555                 560

gag aga gat gat tta aaa aac aaa ttg aaa gcg gaa gaa gag aaa gga     2206
Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu Glu Glu Lys Gly
        565                 570                 575

aat gat ctc ctg tca aga gtt aat atg ttg aaa aat agg ctt caa tca     2254
Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn Arg Leu Gln Ser
    580                 585                 590

ttg gaa gca att gag aaa gat ttc cta aaa aac aaa tta aat caa gac     2302
Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys Leu Asn Gln Asp
595                 600                 605                 610

tct ggg aaa tcc aca aca gca tta cac caa gaa aac aat aag att aag     2350
Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn Asn Lys Ile Lys
                615                 620                 625

gag ctc tct caa gaa gtg gaa aga ctg aaa ctg aag cta aag gac atg     2398
Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys Leu Lys Asp Met
            630                 635                 640

aaa gcc att gag gat gac ctc atg aaa aca gaa gat gaa tat gag act     2446
Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp Glu Tyr Glu Thr
        645                 650                 655

cta gaa cga agg tat gct aat gaa cga gac aaa gct caa ttt tta tct     2494
Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala Gln Phe Leu Ser
    660                 665                 670

aaa gag cta gaa cat gtt aaa atg gaa ctt gct aag tac aag tta gca     2542
Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys Tyr Lys Leu Ala
675                 680                 685                 690
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gaa aag aca gag acc agc cat gaa caa tgg ctt ttc aaa agg ctt caa     2590
Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe Lys Arg Leu Gln
                695                 700                 705

gaa gaa gaa gct aag tca ggg cac ctc tca aga gaa gtg gat gca tta     2638
Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu Val Asp Ala Leu
            710                 715                 720

aaa gag aaa att cat gaa tac atg gca act gaa gac cta ata tgt cac     2686
Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp Leu Ile Cys His
        725                 730                 735

ctc cag gga gat cac tca gtc ctg caa aaa aaa act aaa tca aca aga     2734
Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys Thr Lys Ser Thr Arg
    740                 745                 750

aaa cag gaa cag aga ttt agg aag aga gat tga aaacctcact aaggagttag   2787
Lys Gln Glu Gln Arg Phe Arg Lys Arg Asp
755                 760

agaggtaccg gcatttcagt aagagcctca ggcctagtct caatggaaga agaatttccg   2847

atcctcaagt attttctaaa gaagttcaga cagaagcagt agacaatgaa ccacctgatt   2907

acaagagcct cattcctctg gaacgtgcag tcatcaatgg tcagttatat gaggagagtg   2967

agaatcaaga cgaggaccct aatgatgagg gatctgtgct gtccttcaaa tgcagccagt   3027

ctactccatg tcctgttaac agaaagctat ggattccctg gatgaaatcc aaggagggcc   3087

atcttcagaa tggaaaaatg caaactaaac ccaatgccaa ctttgtgcaa cctggagatc   3147

tagtcctaag ccacacacct gggcagccac ttcatataaa ggttactcca gaccatgtac   3207

aaaacacagc cactcttgaa atcacaagtc caaccacaga gagtcctcac tcttacacga   3267

gtactgcagt gataccgaac tgtggcacgc caaagcaaag gataaccatc ctccaaaacg   3327

cctccataac accagtaaag tccaaaacct ctaccgaaga cctcatgaat ttagaacaag   3387

gcatgtcccc aattaccatg gcaacctttg ccagagcaca gaccccagag tcttgtggtt   3447

ctctaactcc agaaaggaca atgtccccta ttcaggtttt ggctgtgact ggttcagcta   3507

gctctcctga gcagggacgc tccccagaac caacagaaat cagtgccaag catgcgatat   3567

tcagagtctc cccagaccgg cagtcatcat ggcagtttca gcgttcaaac agcaatagct   3627

caagtgtgat aactactgag gataataaaa tccacattca cttaggaagt ccttacatgc   3687

aagctgtagc cagccctgtg agacctgcca gcccttcagc accactgcag gataaccgaa   3747

ctcaaggctt aattaacggg gcactaaaca aaacaaccaa taaagtcacc agcagtatta   3807

ctatcacacc aacagccaca cctcttcctc gacaatcaca aattacagtg gaaccacttc   3867

ttctgcctca ttgaactcaa catccttcag acttttaagg cattccaaat cccagtcttc   3927
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aaaaaaaaaa a 3998

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Pro Arg His Thr Lys Gly His Ser Phe Gln Gly Pro Lys Asn Met Lys
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His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val Ile Leu
35 40 45

Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His Gln Ala
50 55 60

Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile Leu Glu
65 70 75 80

Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu
85 90 95

Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro
100 105 110

Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser
115 120 125

Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp
130 135 140

Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln
145 150 155 160

Leu Leu Val Ala Glu Lys Ser Arg Arg Gln Thr Ile Leu Glu Leu Glu
165 170 175

Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe
180 185 190

Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp
195 200 205

Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg
210 215 220

Val Thr Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser Phe Ala Leu
225 230 235 240

Met Val Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln
245 250 255

Arg Gln Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr
260 265 270

Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala
275 280 285

Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln
290 295 300

Asp Gln Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp Ser Gln Asn
305 310 315 320

Arg Gln Leu Gln Gln Lys Leu Ala Ala Leu Ser Arg Gln Ile Asp Glu
325 330 335

Leu Glu Glu Thr Asn Arg Ser Leu Arg Lys Ala Glu Glu Glu Leu Gln
340 345 350

Asp Ile Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn Ala Gly Ile
355 360 365

Met Ala Glu Val Glu Glu Leu Arg Lys Arg Val Leu Asp Met Glu Gly
370 375 380

Lys Asp Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp Leu Asn
385 390 395 400

Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys Leu Glu

405 410 415

Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu Glu Asp
420 425 430

Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys Asn Leu
435 440 445

Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu Glu Ser
450 455 460

Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg Leu Glu
465 470 475 480

Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys Thr Leu
485 490 495

Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys Leu Lys
500 505 510

Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln Val Glu
515 520 525

Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu Thr Lys
530 535 540

Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr Ser Val
545 550 555 560

Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu Glu Glu
565 570 575

Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn Arg Leu
580 585 590

Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys Leu Asn
595 600 605

Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn Asn Lys
610 615 620

Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys Leu Lys
625 630 635 640

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Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp Glu Tyr
                645                 650                 655

Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala Gln Phe
            660                 665                 670

Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys Tyr Lys
        675                 680                 685

Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe Lys Arg
    690                 695                 700

Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu Val Asp
705                 710                 715                 720

Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp Leu Ile
                725                 730                 735

Cys His Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys Thr Lys Ser
            740                 745                 750

Thr Arg Lys Gln Glu Gln Arg Phe Arg Lys Arg Asp
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         1               5                  10

aaa ttt cca aga cat act aaa ggc cac agt ttc caa ggg cct aaa aac      98
Lys Phe Pro Arg His Thr Lys Gly His Ser Phe Gln Gly Pro Lys Asn
15                  20                  25                  30
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atg aag cat aga cag caa gac aaa gac tcc ccc agt gag tcg gat gta      146
Met Lys His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val
                35                  40                  45

ata ctt ccg tgt ccc aag gca gag aag cca cac agt ggt aat ggc cac      194
Ile Leu Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His
            50                  55                  60

caa gca gaa gac ctc tca aga gat gac ctg tta ttt ctc ctc agc att      242
Gln Ala Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile
        65                  70                  75

ctg gag gga gaa ctg cag gct cga gat gag gtc ata ggc att tta aag      290
Leu Glu Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys
    80                  85                  90

gct gaa aaa atg gac ctg gct ttg ctg gaa gct cag tat ggg ttt gtc      338
Ala Glu Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val
95                  100                 105                 110

act cca aaa aag gtg tta gag gct ctc cag aga gat gct ttt caa gcg      386
Thr Pro Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala
                115                 120                 125

aaa tct acc cct tgg cag gag gac atc tat gag aaa cca atg aat gag      434
Lys Ser Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu
            130                 135                 140

ttg gac aaa gtt gtg gaa aaa cat aaa gaa tct tac aga cga atc ctg      482
Leu Asp Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu
        145                 150                 155

gga cag ctt tta gtg gca gaa aaa tcc cgt agg caa acc ata ttg gag      530
Gly Gln Leu Leu Val Ala Glu Lys Ser Arg Arg Gln Thr Ile Leu Glu
    160                 165                 170

ttg gag gaa gaa aag aga aaa cat aaa gaa tac atg gag aag agt gat      578
Leu Glu Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp
175                 180                 185                 190

gaa ttc ata tgc cta cta gaa cag gaa tgt gaa aga tta aag aag cta      626
Glu Phe Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu
                195                 200                 205

att gat caa gaa atc aag tct cag gag gag aag gag caa gaa aag gag      674
Ile Asp Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu
            210                 215                 220

aaa agg gtc acc acc ctg aaa gag gag ctg acc aag ctg aag tct ttt      722
Lys Arg Val Thr Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser Phe
        225                 230                 235

gct ttg atg gtg gtg gat gaa cag caa agg ctg acg gca cag ctc acc      770
Ala Leu Met Val Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr
    240                 245                 250
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ctt caa aga cag aaa atc caa gag ctg acc aca aat gca aag gaa aca      818
Leu Gln Arg Gln Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr
255                 260                 265                 270

cat acc aaa cta gcc ctt gct gaa gcc aga gtt cag gag gaa gag cag      866
His Thr Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln
                275                 280                 285

aag gca acc aga cta gag aag gaa ctg caa acg cag acc aca aag ttt      914
Lys Ala Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe
            290                 295                 300

cac caa gac caa gac aca att atg gcg aag ctc acc aat gag gac agt      962
His Gln Asp Gln Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp Ser
        305                 310                 315

caa aat cgc cag ctt caa caa aag ctg gca gca ctc agc cgg cag att     1010
Gln Asn Arg Gln Leu Gln Gln Lys Leu Ala Ala Leu Ser Arg Gln Ile
    320                 325                 330

gat gag tta gaa gag aca aac agg tct tta cga aaa gca gaa gag gag     1058
Asp Glu Leu Glu Glu Thr Asn Arg Ser Leu Arg Lys Ala Glu Glu Glu
335                 340                 345                 350

ctg caa gat ata aaa gaa aaa atc agt aag gga gaa tat gga aac gct     1106
Leu Gln Asp Ile Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn Ala
                355                 360                 365

ggt atc atg gct gaa gtg gaa gag ctc agg aaa cgt gtg cta gat atg     1154
Gly Ile Met Ala Glu Val Glu Glu Leu Arg Lys Arg Val Leu Asp Met
            370                 375                 380

gaa ggg aaa gat gaa gag ctc ata aaa atg gag gag cag tgc aga gat     1202
Glu Gly Lys Asp Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp
        385                 390                 395

ctc aat aag agg ctt gaa agg gag acg tta cag agt aaa gac ttt aaa     1250
Leu Asn Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys
    400                 405                 410

cta gag gtt gaa aaa ctc agt aaa aga att atg gct ctg gaa aag tta     1298
Leu Glu Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu
415                 420                 425                 430

gaa gac gct ttc aac aaa agc aaa caa gaa tgc tac tct ctg aaa tgc     1346
Glu Asp Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys
                435                 440                 445

aat tta gaa aaa gaa agg atg acc aca aag cag ttg tct caa gaa ctg     1394
Asn Leu Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu
            450                 455                 460

gag agt tta aaa gta agg atc aaa gag cta gaa gcc att gaa agt cgg     1442
Glu Ser Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg
        465                 470                 475

cta gaa aag aca gaa ttc act cta aaa gag gat tta act aaa ctg aaa     1490
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Leu Glu Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys
    480                 485                 490

aca tta act gtg atg ttt gta gat gaa cgg aaa aca atg agt gaa aaa    1538
Thr Leu Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys
495                 500                 505                 510

tta aag aaa act gaa gat aaa tta caa gct gct tct tct cag ctt caa    1586
Leu Lys Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln
                515                 520                 525

gtg gag caa aat aaa gta aca aca gtt act gag aag tta att gag gaa    1634
Val Glu Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu
            530                 535                 540

act aaa agg gcg ctc aag tcc aaa acc gat gta gaa gaa aag atg tac    1682
Thr Lys Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr
        545                 550                 555

agc gta acc aag gag aga gat gat tta aaa aac aaa ttg aaa gcg gaa    1730
Ser Val Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu
    560                 565                 570

gaa gag aaa gga aat gat ctc ctg tca aga gtt aat atg ttg aaa aat    1778
Glu Glu Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn
575                 580                 585                 590

agg ctt caa tca ttg gaa gca att gag aaa gat ttc cta aaa aac aaa    1826
Arg Leu Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys
                595                 600                 605

tta aat caa gac tct ggg aaa tcc aca aca gca tta cac caa gaa aac    1874
Leu Asn Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn
            610                 615                 620

aat aag att aag gag ctc tct caa gaa gtg gaa aga ctg aaa ctg aag    1922
Asn Lys Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys
        625                 630                 635

cta aag gac atg aaa gcc att gag gat gac ctc atg aaa aca gaa gat    1970
Leu Lys Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp
    640                 645                 650

gaa tat gag act cta gaa cga agg tat gct aat gaa cga gac aaa gct    2018
Glu Tyr Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala
655                 660                 665                 670

caa ttt tta tct aaa gag cta gaa cat gtt aaa atg gaa ctt gct aag    2066
Gln Phe Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys
                675                 680                 685

tac aag tta gca gaa aag aca gag acc agc cat gaa caa tgg ctt ttc    2114
Tyr Lys Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe
            690                 695                 700

aaa agg ctt caa gaa gaa gaa gct aag tca ggg cac ctc tca aga gaa    2162
Lys Arg Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu
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        705                 710                 715

gtg gat gca tta aaa gag aaa att cat gaa tac atg gca act gaa gac     2210
Val Asp Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp
    720                 725                 730

cta ata tgt cac ctc cag gga gat cac tca gtc ctg caa aaa aaa cta     2258
Leu Ile Cys His Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys Leu
735                 740                 745                 750

aat caa caa gaa aac agg aac aga gat tta gga aga gag att gaa aac     2306
Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu Asn
                755                 760                 765

ctc act aag gag tta gag agg tac cgg cat ttc agt aag agc ctc agg     2354
Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu Arg
        770                 775                 780

cct agt ctc aat gga aga aga att tcc gat cct caa gta ttt tct aaa     2402
Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys
785                 790                 795

gaa gtt cag aca gaa gca gta gac aat gaa cca cct gat tac aag agc     2450
Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys Ser
    800                 805                 810

ctc att cct ctg gaa cgt gca gtc atc aat ggt cag tta tat gag gag     2498
Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu Glu
815                 820                 825                 830

agt gag aat caa gac gag gac cct aat gat gag gga tct gtg ctg tcc     2546
Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu Ser
                835                 840                 845

ttc aaa tgc agc cag tct act cca tgt cct gtt aac aga aag cta tgg     2594
Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu Trp
            850                 855                 860

att ccc tgg atg aaa tcc aag gag ggc cat ctt cag aat gga aaa atg     2642
Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys Met
        865                 870                 875

caa act aaa ccc aat gcc aac ttt gtg caa cct gga gat cta gtc cta     2690
Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val Leu
    880                 885                 890

agc cac aca cct ggg cag cca ctt cat ata aag gtt act cca gac cat     2738
Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp His
895                 900                 905                 910

gta caa aac aca gcc act ctt gaa atc aca agt cca acc aca gag agt     2786
Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu Ser
                915                 920                 925

cct cac tct tac acg agt act gca gtg ata ccg aac tgt ggc acg cca     2834
Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro
            930                 935                 940
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aag caa agg ata acc atc ctc caa aac gcc tcc ata aca cca gta aag     2882
Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val Lys
        945                 950                 955

tcc aaa acc tct acc gaa gac ctc atg aat tta gaa caa ggc atg tcc     2930
Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser
    960                 965                 970

cca att acc atg gca acc ttt gcc aga gca cag acc cca gag tct tgt     2978
Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser Cys
975                 980                 985                 990

ggt tct cta act cca gaa agg aca atg tcc  cct att cag gtt ttg  gct   3026
Gly Ser Leu Thr Pro Glu Arg Thr Met Ser  Pro Ile Gln Val Leu  Ala
                995                 1000                1005

gtg act ggt tca  gct agc tct cct gag  cag gga cgc tcc cca  gaa      3071
Val Thr Gly Ser  Ala Ser Ser Pro Glu  Gln Gly Arg Ser Pro  Glu
            1010                1015                1020

cca aca gaa atc  agt gcc aag cat gcg  ata ttc aga gtc tcc  cca      3116
Pro Thr Glu Ile  Ser Ala Lys His Ala  Ile Phe Arg Val Ser  Pro
            1025                1030                1035

gac cgg cag tca  tca tgg cag ttt cag  cgt tca aac agc aat  agc      3161
Asp Arg Gln Ser  Ser Trp Gln Phe Gln  Arg Ser Asn Ser Asn  Ser
            1040                1045                1050

tca agt gtg ata  act act gag gat aat  aaa atc cac att cac  tta      3206
Ser Ser Val Ile  Thr Thr Glu Asp Asn  Lys Ile His Ile His  Leu
            1055                1060                1065

gga agt cct tac  atg caa gct gta gcc  agc cct gtg aga cct  gcc      3251
Gly Ser Pro Tyr  Met Gln Ala Val Ala  Ser Pro Val Arg Pro  Ala
            1070                1075                1080

agc cct tca gca  cca ctg cag gat aac  cga act caa ggc tta  att      3296
Ser Pro Ser Ala  Pro Leu Gln Asp Asn  Arg Thr Gln Gly Leu  Ile
            1085                1090                1095

aac ggg gca cta  aac aaa aca acc aat  aaa gtc acc agc agt  att      3341
Asn Gly Ala Leu  Asn Lys Thr Thr Asn  Lys Val Thr Ser Ser  Ile
            1100                1105                1110

act atc aca cca  aca gcc aca cct ctt  cct cga caa tca caa  att      3386
Thr Ile Thr Pro  Thr Ala Thr Pro Leu  Pro Arg Gln Ser Gln  Ile
            1115                1120                1125

aca gtg gaa cca  ctt ctt ctg cct cat  tgaactcaac atccttc           3430
Thr Val Glu Pro  Leu Leu Leu Pro His
            1130                1135
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Met Arg Ser Arg Gly Ser Asp Thr Glu Gly Ser Ala Gln Lys Lys Phe
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Pro Arg His Thr Lys Gly His Ser Phe Gln Gly Pro Lys Asn Met Lys
            20                  25                  30

His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val Ile Leu
        35                  40                  45

Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His Gln Ala
    50                  55                  60

Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile Leu Glu
65                  70                  75                  80

Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu
                85                  90                  95

Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro
            100                 105                 110

Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser
        115                 120                 125

Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp
    130                 135                 140

Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln
145                 150                 155                 160

Leu Leu Val Ala Glu Lys Ser Arg Arg Gln Thr Ile Leu Glu Leu Glu
                165                 170                 175

Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe
            180                 185                 190

Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp
        195                 200                 205

Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg
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    210                 215                 220

Val Thr Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser Phe Ala Leu
225                 230                 235                 240

Met Val Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln
                245                 250                 255

Arg Gln Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr
            260                 265                 270

Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala
        275                 280                 285

Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln
    290                 295                 300

Asp Gln Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp Ser Gln Asn
305                 310                 315                 320

Arg Gln Leu Gln Gln Lys Leu Ala Ala Leu Ser Arg Gln Ile Asp Glu
                325                 330                 335

Leu Glu Glu Thr Asn Arg Ser Leu Arg Lys Ala Glu Glu Glu Leu Gln
            340                 345                 350

Asp Ile Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn Ala Gly Ile
        355                 360                 365

Met Ala Glu Val Glu Glu Leu Arg Lys Arg Val Leu Asp Met Glu Gly
    370                 375                 380

Lys Asp Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp Leu Asn
385                 390                 395                 400

Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys Leu Glu
                405                 410                 415

Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu Glu Asp
            420                 425                 430

Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys Asn Leu
        435                 440                 445
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Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu Glu Ser
    450                 455                 460

Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg Leu Glu
465                 470                 475                 480

Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys Thr Leu
                485                 490                 495

Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys Leu Lys
            500                 505                 510

Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln Val Glu
        515                 520                 525

Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu Thr Lys
    530                 535                 540

Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr Ser Val
545                 550                 555                 560

Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu Glu Glu
                565                 570                 575

Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn Arg Leu
            580                 585                 590

Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys Leu Asn
        595                 600                 605

Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn Asn Lys
    610                 615                 620

Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys Leu Lys
625                 630                 635                 640

Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp Glu Tyr
                645                 650                 655

Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala Gln Phe
            660                 665                 670
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Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys Tyr Lys
        675                 680                 685

Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe Lys Arg
    690                 695                 700

Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu Val Asp
705                 710                 715                 720

Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp Leu Ile
                725                 730                 735

Cys His Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys Leu Asn Gln
            740                 745                 750

Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu Asn Leu Thr
        755                 760                 765

Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu Arg Pro Ser
    770                 775                 780

Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys Glu Val
785                 790                 795                 800

Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys Ser Leu Ile
                805                 810                 815

Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu Glu Ser Glu
            820                 825                 830

Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu Ser Phe Lys
        835                 840                 845

Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu Trp Ile Pro
    850                 855                 860

Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys Met Gln Thr
865                 870                 875                 880

Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val Leu Ser His
                885                 890                 895
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Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp His Val Gln
900 905 910

Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu Ser Pro His
915 920 925

Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro Lys Gln
930 935 940

Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val Lys Ser Lys
945 950 955 960

Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser Pro Ile
965 970 975

Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser Cys Gly Ser
980 985 990

Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu Ala Val Thr
995 1000 1005

Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu Pro Thr
1010 1015 1020

Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp Arg
1025 1030 1035

Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser
1040 1045 1050

Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser
1055 1060 1065

Pro Tyr Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro
1070 1075 1080

Ser Ala Pro Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly
1085 1090 1095

Ala Leu Asn Lys Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile
1100 1105 1110

Thr Pro Thr Ala Thr Pro Leu Pro Arg Gln Ser Gln Ile Thr Val

1115 1120 1125

Glu Pro Leu Leu Leu Pro His
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Met Arg Ser Arg Gly Ser Asp Thr Glu Gly Ser Ala Gln
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aag aaa ttt cca aga cat act aaa ggc cac agt ttc caa ggg cct aaa 98
Lys Lys Phe Pro Arg His Thr Lys Gly His Ser Phe Gln Gly Pro Lys
15 20 25

aac atg aag cat aga cag caa gac aaa gac tcc ccc agt gag tcg gat 146
Asn Met Lys His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp
30 35 40 45

gta ata ctt ccg tgt ccc aag gca gag aag cca cac agt ggt aat ggc 194
Val Ile Leu Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly
50 55 60

cac caa gca gaa gac ctc tca aga gat gac ctg tta ttt ctc ctc agc 242
His Gln Ala Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser
65 70 75

att ctg gag gga gaa ctg cag gct cga gat gag gtc ata ggc att tta 290
Ile Leu Glu Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu
80 85 90

aag gct gaa aaa atg gac ctg gct ttg ctg gaa gct cag tat ggg ttt 338
Lys Ala Glu Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe
95 100 105

gtc act cca aaa aag gtg tta gag gct ctc cag aga gat gct ttt caa 386
Val Thr Pro Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln
110 115 120 125

gcg aaa tct acc cct tgg cag gag gac atc tat gag aaa cca atg aat 434
Ala Lys Ser Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn

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                130                 135                 140

gag ttg gac aaa gtt gtg gaa aaa cat aaa gaa tct tac aga cga atc      482
Glu Leu Asp Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile
            145                 150                 155

ctg gga cag ctt tta gtg gca gaa aaa tcc cat agg caa acc ata ttg      530
Leu Gly Gln Leu Leu Val Ala Glu Lys Ser His Arg Gln Thr Ile Leu
        160                 165                 170

gag ttg gag gaa gaa aag aga aaa cat aaa gaa tac atg gag aag agt      578
Glu Leu Glu Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser
    175                 180                 185

gat gaa ttc ata tgc cta cta gaa cag gaa tgt gaa aga tta aag aag      626
Asp Glu Phe Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys
190                 195                 200                 205

cta att gat caa gaa atc aag tct cag gag gag aag gag caa gaa aag      674
Leu Ile Asp Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys
                210                 215                 220

gag aaa agg gtc acc acc ctg aaa gag gag ctg acc aag ctg aag tct      722
Glu Lys Arg Val Thr Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser
            225                 230                 235

ttt gct ttg atg gtg gtg gat gaa cag caa agg ctg acg gca cag ctc      770
Phe Ala Leu Met Val Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu
        240                 245                 250

acc ctt caa aga cag aaa atc caa gag ctg acc aca aat gca aag gaa      818
Thr Leu Gln Arg Gln Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu
    255                 260                 265

aca cat acc aaa cta gcc ctt gct gaa gcc aga gtt cag gag gaa gag      866
Thr His Thr Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu
270                 275                 280                 285

cag aag gca acc aga cta gag aag gaa ctg caa acg cag acc aca aag      914
Gln Lys Ala Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys
                290                 295                 300

ttt cac caa gac caa gac aca att atg gcg aag ctc acc aat gag gac      962
Phe His Gln Asp Gln Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp
            305                 310                 315

agt caa aat cgc cag ctt caa caa aag ctg gca gca ctc agc cgg cag     1010
Ser Gln Asn Arg Gln Leu Gln Gln Lys Leu Ala Ala Leu Ser Arg Gln
        320                 325                 330

att gat gag tta gaa gag aca aac agg tct tta cga aaa gca gaa gag     1058
Ile Asp Glu Leu Glu Glu Thr Asn Arg Ser Leu Arg Lys Ala Glu Glu
    335                 340                 345

gag ctg caa gat ata aaa gaa aaa atc agt aag gga gaa tat gga aac     1106
Glu Leu Gln Asp Ile Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn
350                 355                 360                 365
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gct ggt atc atg gct gaa gtg gaa gag ctc agg aaa cgt gtg cta gat     1154
Ala Gly Ile Met Ala Glu Val Glu Glu Leu Arg Lys Arg Val Leu Asp
                370                 375                 380

atg gaa ggg aaa gat gaa gag ctc ata aaa atg gag gag cag tgc aga     1202
Met Glu Gly Lys Asp Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg
            385                 390                 395

gat ctc aat aag agg ctt gaa agg gag acg tta cag agt aaa gac ttt     1250
Asp Leu Asn Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe
        400                 405                 410

aaa cta gag gtt gaa aaa ctc agt aaa aga att atg gct ctg gaa aag     1298
Lys Leu Glu Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys
    415                 420                 425

tta gaa gac gct ttc aac aaa agc aaa caa gaa tgc tac tct ctg aaa     1346
Leu Glu Asp Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys
430                 435                 440                 445

tgc aat tta gaa aaa gaa agg atg acc aca aag cag ttg tct caa gaa     1394
Cys Asn Leu Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu
                450                 455                 460

ctg gag agt tta aaa gta agg atc aaa gag cta gaa gcc att gaa agt     1442
Leu Glu Ser Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser
            465                 470                 475

cgg cta gaa aag aca gaa ttc act cta aaa gag gat tta act aaa ctg     1490
Arg Leu Glu Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu
        480                 485                 490

aaa aca tta act gtg atg ttt gta gat gaa cgg aaa aca atg agt gaa     1538
Lys Thr Leu Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu
    495                 500                 505

aaa tta aag aaa act gaa gat aaa tta caa gct gct tct tct cag ctt     1586
Lys Leu Lys Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu
510                 515                 520                 525

caa gtg gag caa aat aaa gta aca aca gtt act gag aag tta att gag     1634
Gln Val Glu Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu
                530                 535                 540

gaa act aaa agg gcg ctc aag tcc aaa acc gat gta gaa gaa aag atg     1682
Glu Thr Lys Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met
            545                 550                 555

tac agc gta acc aag gag aga gat gat tta aaa aac aaa ttg aaa gcg     1730
Tyr Ser Val Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala
        560                 565                 570

gaa gaa gag aaa gga aat gat ctc ctg tca aga gtt aat atg ttg aaa     1778
Glu Glu Glu Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys
    575                 580                 585
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aat agg ctt caa tca ttg gaa gca att gag aaa gat ttc cta aaa aac     1826
Asn Arg Leu Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn
590                 595                 600                 605

aaa tta aat caa gac tct ggg aaa tcc aca aca gca tta cac caa gaa     1874
Lys Leu Asn Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu
                610                 615                 620

aac aat aag att aag gag ctc tct caa gaa gtg gaa aga ctg aaa ctg     1922
Asn Asn Lys Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu
            625                 630                 635

aag cta aag gac atg aaa gcc att gag gat gac ctc atg aaa aca gaa     1970
Lys Leu Lys Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu
        640                 645                 650

gat gaa tat gag act cta gaa cga agg tat gct aat gaa cga gac aaa     2018
Asp Glu Tyr Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys
    655                 660                 665

gct caa ttt tta tct aaa gag cta gaa cat gtt aaa atg gaa ctt gct     2066
Ala Gln Phe Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala
670                 675                 680                 685

aag tac aag tta gca gaa aag aca gag acc agc cat gaa caa tgg ctt     2114
Lys Tyr Lys Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu
                690                 695                 700

ttc aaa agg ctt caa gaa gaa gaa gct aag tca ggg cac ctc tca aga     2162
Phe Lys Arg Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg
            705                 710                 715

gaa gtg gat gca tta aaa gag aaa att cat gaa tac atg gca act gaa     2210
Glu Val Asp Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu
        720                 725                 730

gac cta ata tgt cac ctc cag gga gat cac tca gtc ctg caa aaa aaa     2258
Asp Leu Ile Cys His Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys
    735                 740                 745

cta aat caa caa gaa aac agg aac aga gat tta gga aga gag att gaa     2306
Leu Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu
750                 755                 760                 765

aac ctc act aag gag tta gag agg tac cgg cat ttc agt aag agc ctc     2354
Asn Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu
                770                 775                 780

agg cct agt ctc aat gga aga aga att tcc gat cct caa gta ttt tct     2402
Arg Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser
            785                 790                 795

aaa gaa gtt cag aca gaa gca gta gac aat gaa cca cct gat tac aag     2450
Lys Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys
        800                 805                 810

agc ctc att cct ctg gaa cgt gca gtc atc aat ggt cag tta tat gag     2498
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Ser Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu
    815                 820                 825

gag agt gag aat caa gac gag gac cct aat gat gag gga tct gtg ctg    2546
Glu Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu
830                 835                 840                 845

tcc ttc aaa tgc agc cag tct act cca tgt cct gtt aac aga aag cta    2594
Ser Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu
                850                 855                 860

tgg att ccc tgg atg aaa tcc aag gag ggc cat ctt cag aat gga aaa    2642
Trp Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys
            865                 870                 875

atg caa act aaa ccc aat gcc aac ttt gtg caa cct gga gat cta gtc    2690
Met Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val
        880                 885                 890

cta agc cac aca cct ggg cag cca ctt cat ata aag gtt act cca gac    2738
Leu Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp
    895                 900                 905

cat gta caa aac aca gcc act ctt gaa atc aca agt cca acc aca gag    2786
His Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu
910                 915                 920                 925

agt cct cac tct tac acg agt act gca gtg ata ccg aac tgt ggc acg    2834
Ser Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr
                930                 935                 940

cca aag caa agg ata acc atc ctc caa aac gcc tcc ata aca cca gta    2882
Pro Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val
            945                 950                 955

aag tcc aaa acc tct acc gaa gac ctc atg aat tta gaa caa ggc atg    2930
Lys Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met
        960                 965                 970

tcc cca att acc atg gca acc ttt gcc aga gca cag acc cca gag tct    2978
Ser Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser
    975                 980                 985

tgt ggt tct cta act cca gaa agg aca atg tcc  cct att cag gtt ttg    3026
Cys Gly Ser Leu Thr Pro Glu Arg Thr Met Ser  Pro Ile Gln Val Leu
990                 995                 1000                1005

gct gtg act ggt tca  gct agc tct cct gag  cag gga cgc tcc cca       3071
Ala Val Thr Gly Ser  Ala Ser Ser Pro Glu  Gln Gly Arg Ser Pro
                1010                1015                1020

gaa cca aca gaa atc  agt gcc aag cat gcg  ata ttc aga gtc tcc       3116
Glu Pro Thr Glu Ile  Ser Ala Lys His Ala  Ile Phe Arg Val Ser
                1025                1030                1035

cca gac cgg cag tca  tca tgg cag ttt cag  cgt tca aac agc aat       3161
Pro Asp Arg Gln Ser  Ser Trp Gln Phe Gln  Arg Ser Asn Ser Asn
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```
                1040                1045                1050

agc tca agt gtg ata  act act gag gat aat  aaa atc cac att cac      3206
Ser Ser Ser Val Ile  Thr Thr Glu Asp Asn  Lys Ile His Ile His
                1055                1060                1065

tta gga agt cct tac  atg caa gct gta gcc  agc cct gtg aga cct      3251
Leu Gly Ser Pro Tyr  Met Gln Ala Val Ala  Ser Pro Val Arg Pro
                1070                1075                1080

gcc agc cct tca gca  cca ctg cag gat aac  cga act caa ggc tta      3296
Ala Ser Pro Ser Ala  Pro Leu Gln Asp Asn  Arg Thr Gln Gly Leu
                1085                1090                1095

att aac ggg gca cta  aac aaa aca acc aat  aaa gtc acc agc agt      3341
Ile Asn Gly Ala Leu  Asn Lys Thr Thr Asn  Lys Val Thr Ser Ser
                1100                1105                1110

att act atc aca cca  aca gcc aca cct ctt  cct cga caa tca caa      3386
Ile Thr Ile Thr Pro  Thr Ala Thr Pro Leu  Pro Arg Gln Ser Gln
                1115                1120                1125

att aca gta agt aat  ata tat aac tgacc                            3415
Ile Thr Val Ser Asn  Ile Tyr Asn
                1130
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Met Arg Ser Arg Gly Ser Asp Thr Glu Gly Ser Ala Gln Lys Lys Phe
1               5                  10                  15

Pro Arg His Thr Lys Gly His Ser Phe Gln Gly Pro Lys Asn Met Lys
            20                  25                  30

His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val Ile Leu
        35                  40                  45

Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His Gln Ala
    50                  55                  60

Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile Leu Glu
65                  70                  75                  80

Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu
                85                  90                  95
```

```
Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro
            100                 105                 110

Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser
        115                 120                 125

Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp
    130                 135                 140

Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln
145                 150                 155                 160

Leu Leu Val Ala Glu Lys Ser His Arg Gln Thr Ile Leu Glu Leu Glu
                165                 170                 175

Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe
            180                 185                 190

Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp
        195                 200                 205

Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg
    210                 215                 220

Val Thr Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser Phe Ala Leu
225                 230                 235                 240

Met Val Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln
                245                 250                 255

Arg Gln Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr
            260                 265                 270

Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala
        275                 280                 285

Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln
    290                 295                 300

Asp Gln Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp Ser Gln Asn
305                 310                 315                 320
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Arg Gln Leu Gln Gln Lys Leu Ala Ala Leu Ser Arg Gln Ile Asp Glu
325 330 335

Leu Glu Glu Thr Asn Arg Ser Leu Arg Lys Ala Glu Glu Glu Leu Gln
340 345 350

Asp Ile Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn Ala Gly Ile
355 360 365

Met Ala Glu Val Glu Glu Leu Arg Lys Arg Val Leu Asp Met Glu Gly
370 375 380

Lys Asp Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp Leu Asn
385 390 395 400

Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys Leu Glu
405 410 415

Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu Glu Asp
420 425 430

Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys Asn Leu
435 440 445

Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu Glu Ser
450 455 460

Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg Leu Glu
465 470 475 480

Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys Thr Leu
485 490 495

Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys Leu Lys
500 505 510

Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln Val Glu
515 520 525

Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu Thr Lys
530 535 540

Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr Ser Val

545 550 555 560

Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu Glu Glu
565 570 575

Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn Arg Leu
580 585 590

Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys Leu Asn
595 600 605

Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn Asn Lys
610 615 620

Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys Leu Lys
625 630 635 640

Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp Glu Tyr
645 650 655

Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala Gln Phe
660 665 670

Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys Tyr Lys
675 680 685

Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe Lys Arg
690 695 700

Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu Val Asp
705 710 715 720

Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp Leu Ile
725 730 735

Cys His Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys Leu Asn Gln
740 745 750

Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu Asn Leu Thr
755 760 765

Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu Arg Pro Ser
770 775 780

```
Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys Glu Val
785                 790                 795                 800

Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys Ser Leu Ile
                805                 810                 815

Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu Glu Ser Glu
            820                 825                 830

Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu Ser Phe Lys
        835                 840                 845

Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu Trp Ile Pro
    850                 855                 860

Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys Met Gln Thr
865                 870                 875                 880

Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val Leu Ser His
                885                 890                 895

Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp His Val Gln
            900                 905                 910

Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu Ser Pro His
        915                 920                 925

Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro Lys Gln
    930                 935                 940

Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val Lys Ser Lys
945                 950                 955                 960

Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser Pro Ile
                965                 970                 975

Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser Cys Gly Ser
            980                 985                 990

Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu Ala Val Thr
        995                 1000                1005
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Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu Pro Thr
1010 1015 1020

Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp Arg
1025 1030 1035

Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser
1040 1045 1050

Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser
1055 1060 1065

Pro Tyr Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro
1070 1075 1080

Ser Ala Pro Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly
1085 1090 1095

Ala Leu Asn Lys Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile
1100 1105 1110

Thr Pro Thr Ala Thr Pro Leu Pro Arg Gln Ser Gln Ile Thr Val
1115 1120 1125

Ser Asn Ile Tyr Asn
1130

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Met Arg Ser Arg Gly Ser Asp Thr Glu Gly Ser Ala Gln Lys
1 5 10

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aaa ttt cca aga cat act aaa ggc cac agt ttc caa ggg cct aaa aac      98
Lys Phe Pro Arg His Thr Lys Gly His Ser Phe Gln Gly Pro Lys Asn
15                  20                  25                  30

atg aag cat aga cag caa gac aaa gac tcc ccc agt gag tcg gat gta     146
Met Lys His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val
                35                  40                  45

ata ctt ccg tgt ccc aag gca gag aag cca cac agt ggt aat ggc cac     194
Ile Leu Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His
            50                  55                  60

caa gca gaa gac ctc tca aga gat gac ctg tta ttt ctc ctc agc att     242
Gln Ala Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile
        65                  70                  75

ctg gag gga gaa ctg cag gct cga gat gag gtc ata ggc att tta aag     290
Leu Glu Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys
    80                  85                  90

gct gaa aaa atg gac ctg gct ttg ctg gaa gct cag tat ggg ttt gtc     338
Ala Glu Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val
95                  100                 105                 110

act cca aaa aag gtg tta gag gct ctc cag aga gat gct ttt caa gcg     386
Thr Pro Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala
                115                 120                 125

aaa tct acc cct tgg cag gag gac atc tat gag aaa cca atg aat gag     434
Lys Ser Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu
            130                 135                 140

ttg gac aaa gtt gtg gaa aaa cat aaa gaa tct tac aga cga atc ctg     482
Leu Asp Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu
        145                 150                 155

gga cag ctt tta gtg gca gaa aaa tcc cgt agg caa acc ata ttg gag     530
Gly Gln Leu Leu Val Ala Glu Lys Ser Arg Arg Gln Thr Ile Leu Glu
    160                 165                 170

ttg gag gaa gaa aag aga aaa cat aaa gaa tac atg gag aag agt gat     578
Leu Glu Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp
175                 180                 185                 190

gaa ttc ata tgc cta cta gaa cag gaa tgt gaa aga tta aag aag cta     626
Glu Phe Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu
                195                 200                 205

att gat caa gaa atc aag tct cag gag gag aag gag caa gaa aag gag     674
Ile Asp Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu
            210                 215                 220

aaa agg gtc acc acc ctg aaa gag gag ctg acc aag ctg aag tct ttt     722
Lys Arg Val Thr Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser Phe
        225                 230                 235

gct ttg atg gtg gtg gat gaa cag caa agg ctg acg gca cag ctc acc     770
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Ala Leu Met Val Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr
    240                 245                 250

ctt caa aga cag aaa atc caa gag ctg acc aca aat gca aag gaa aca      818
Leu Gln Arg Gln Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr
255                 260                 265                 270

cat acc aaa cta gcc ctt gct gaa gcc aga gtt cag gag gaa gag cag      866
His Thr Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln
                275                 280                 285

aag gca acc aga cta gag aag gaa ctg caa acg cag acc aca aag ttt      914
Lys Ala Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe
            290                 295                 300

cac caa gac caa gac aca att atg gcg aag ctc acc aat gag gac agt      962
His Gln Asp Gln Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp Ser
        305                 310                 315

caa aat cgc cag ctt caa caa aag ctg gca gca ctc agc cgg cag att     1010
Gln Asn Arg Gln Leu Gln Gln Lys Leu Ala Ala Leu Ser Arg Gln Ile
    320                 325                 330

gat gag tta gaa gag aca aac agg tct tta cga aaa gca gaa gag gag     1058
Asp Glu Leu Glu Glu Thr Asn Arg Ser Leu Arg Lys Ala Glu Glu Glu
335                 340                 345                 350

ctg caa gat ata aaa gaa aaa atc agt aag gga gaa tat gga aac gct     1106
Leu Gln Asp Ile Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn Ala
                355                 360                 365

ggt atc atg gct gaa gtg gaa gag ctc agg aaa cgt gtg cta gat atg     1154
Gly Ile Met Ala Glu Val Glu Glu Leu Arg Lys Arg Val Leu Asp Met
            370                 375                 380

gaa ggg aaa gat gaa gag ctc ata aaa atg gag gag cag tgc aga gat     1202
Glu Gly Lys Asp Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp
        385                 390                 395

ctc aat aag agg ctt gaa agg gag acg tta cag agt aaa gac ttt aaa     1250
Leu Asn Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys
    400                 405                 410

cta gag gtt gaa aaa ctc agt aaa aga att atg gct ctg gaa aag tta     1298
Leu Glu Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu
415                 420                 425                 430

gaa gac gct ttc aac aaa agc aaa caa gaa tgc tac tct ctg aaa tgc     1346
Glu Asp Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys
                435                 440                 445

aat tta gaa aaa gaa agg atg acc aca aag cag ttg tct caa gaa ctg     1394
Asn Leu Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu
            450                 455                 460

gag agt tta aaa gta agg atc aaa gag cta gaa gcc att gaa agt cgg     1442
Glu Ser Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg
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        465                 470                 475

cta gaa aag aca gaa ttc act cta aaa gag gat tta act aaa ctg aaa     1490
Leu Glu Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys
    480                 485                 490

aca tta act gtg atg ttt gta gat gaa cgg aaa aca atg agt gaa aaa     1538
Thr Leu Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys
495                 500                 505                 510

tta aag aaa act gaa gat aaa tta caa gct gct tct tct cag ctt caa     1586
Leu Lys Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln
                515                 520                 525

gtg gag caa aat aaa gta aca aca gtt act gag aag tta att gag gaa     1634
Val Glu Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu
            530                 535                 540

act aaa agg gcg ctc aag tcc aaa acc gat gta gaa gaa aag atg tac     1682
Thr Lys Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr
        545                 550                 555

agc gta acc aag gag aga gat gat tta aaa aac aaa ttg aaa gcg gaa     1730
Ser Val Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu
    560                 565                 570

gaa gag aaa gga aat gat ctc ctg tca aga gtt aat atg ttg aaa aat     1778
Glu Glu Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn
575                 580                 585                 590

agg ctt caa tca ttg gaa gca att gag aaa gat ttc cta aaa aac aaa     1826
Arg Leu Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys
                595                 600                 605

tta aat caa gac tct ggg aaa tcc aca aca gca tta cac caa gaa aac     1874
Leu Asn Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn
            610                 615                 620

aat aag att aag gag ctc tct caa gaa gtg gaa aga ctg aaa ctg aag     1922
Asn Lys Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys
        625                 630                 635

cta aag gac atg aaa gcc att gag gat gac ctc atg aaa aca gaa gat     1970
Leu Lys Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp
    640                 645                 650

gaa tat gag act cta gaa cga agg tat gct aat gaa cga gac aaa gct     2018
Glu Tyr Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala
655                 660                 665                 670

caa ttt tta tct aaa gag cta gaa cat gtt aaa atg gaa ctt gct aag     2066
Gln Phe Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys
                675                 680                 685

tac aag tta gca gaa aag aca gag acc agc cat gaa caa tgg ctt ttc     2114
Tyr Lys Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe
            690                 695                 700
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aaa agg ctt caa gaa gaa gaa gct aag tca ggg cac ctc tca aga gaa      2162
Lys Arg Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu
        705                 710                 715

gtg gat gca tta aaa gag aaa att cat gaa tac atg gca act gaa gac      2210
Val Asp Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp
    720                 725                 730

cta ata tgt cac ctc cag gga gat cac tca gtc ctg caa aaa aaa cta      2258
Leu Ile Cys His Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys Leu
735                 740                 745                 750

aat caa caa gaa aac agg aac aga gat tta gga aga gag att gaa aac      2306
Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu Asn
                755                 760                 765

ctc act aag gag tta gag agg tac cgg cat ttc agt aag agc ctc agg      2354
Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu Arg
            770                 775                 780

cct agt ctc aat gga aga aga att tcc gat cct caa gta ttt tct aaa      2402
Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys
        785                 790                 795

gaa gtt cag aca gaa gca gta gac aat gaa cca cct gat tac aag agc      2450
Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys Ser
    800                 805                 810

ctc att cct ctg gaa cgt gca gtc atc aat ggt cag tta tat gag gag      2498
Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu Glu
815                 820                 825                 830

agt gag aat caa gac gag gac cct aat gat gag gga tct gtg ctg tcc      2546
Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu Ser
                835                 840                 845

ttc aaa tgc agc cag tct act cca tgt cct gtt aac aga aag cta tgg      2594
Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu Trp
            850                 855                 860

att ccc tgg atg aaa tcc aag gag ggc cat ctt cag aat gga aaa atg      2642
Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys Met
        865                 870                 875

caa act aaa ccc aat gcc aac ttt gtg caa cct gga gat cta gtc cta      2690
Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val Leu
    880                 885                 890

agc cac aca cct ggg cag cca ctt cat ata aag gtt act cca gac cat      2738
Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp His
895                 900                 905                 910

gta caa aac aca gcc act ctt gaa atc aca agt cca acc aca gag agt      2786
Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu Ser
                915                 920                 925
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cct cac tct tac acg agt act gca gtg ata ccg aac tgt ggc acg cca     2834
Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro
            930                 935                 940

aag caa agg ata acc atc ctc caa aac gcc tcc ata aca cca gta aag     2882
Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val Lys
        945                 950                 955

tcc aaa acc tct acc gaa gac ctc atg aat tta gaa caa ggc atg tcc     2930
Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser
    960                 965                 970

cca att acc atg gca acc ttt gcc aga gca cag acc cca gag tct tgt     2978
Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser Cys
975                 980                 985                 990

ggt tct cta act cca gaa agg aca atg tcc cct att cag gtt ttg gct     3026
Gly Ser Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu Ala
                995                 1000                1005

gtg act ggt tca gct agc tct cct gag cag gga cgc tcc cca gaa         3071
Val Thr Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu
            1010                1015                1020

cca aca gaa atc agt gcc aag cat gcg ata ttc aga gtc tcc cca         3116
Pro Thr Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro
            1025                1030                1035

gac cgg cag tca tca tgg cag ttt cag cgt tca aac agc aat agc         3161
Asp Arg Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser
            1040                1045                1050

tca agt gtg ata act act gag gat aat aaa atc cac att cac tta         3206
Ser Ser Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu
            1055                1060                1065

gga agt cct tac atg caa gct gta gcc agc cct gtg aga cct gcc         3251
Gly Ser Pro Tyr Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala
            1070                1075                1080

agc cct tca gca cca ctg cag gat aac cga act caa ggc tta att         3296
Ser Pro Ser Ala Pro Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile
            1085                1090                1095

aac ggg gca cta aac aaa aca acc aat aaa gtc acc agc agt att         3341
Asn Gly Ala Leu Asn Lys Thr Thr Asn Lys Val Thr Ser Ser Ile
            1100                1105                1110

act atc aca cca aca gcc aca cct ctt cct cga caa tca caa att         3386
Thr Ile Thr Pro Thr Ala Thr Pro Leu Pro Arg Gln Ser Gln Ile
            1115                1120                1125

aca gta agt aat ata tat aac tgaccacgc                              3416
Thr Val Ser Asn Ile Tyr Asn
            1130
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Met Arg Ser Arg Gly Ser Asp Thr Glu Gly Ser Ala Gln Lys Lys Phe
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Pro Arg His Thr Lys Gly His Ser Phe Gln Gly Pro Lys Asn Met Lys
20 25 30

His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val Ile Leu
35 40 45

Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His Gln Ala
50 55 60

Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile Leu Glu
65 70 75 80

Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu
85 90 95

Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro
100 105 110

Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser
115 120 125

Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp
130 135 140

Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln
145 150 155 160

Leu Leu Val Ala Glu Lys Ser Arg Arg Gln Thr Ile Leu Glu Leu Glu
165 170 175

Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe
180 185 190

Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp
195 200 205

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Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg
    210                 215                 220

Val Thr Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser Phe Ala Leu
225                 230                 235                 240

Met Val Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln
                245                 250                 255

Arg Gln Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr
            260                 265                 270

Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala
        275                 280                 285

Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln
    290                 295                 300

Asp Gln Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp Ser Gln Asn
305                 310                 315                 320

Arg Gln Leu Gln Gln Lys Leu Ala Ala Leu Ser Arg Gln Ile Asp Glu
                325                 330                 335

Leu Glu Glu Thr Asn Arg Ser Leu Arg Lys Ala Glu Glu Glu Leu Gln
            340                 345                 350

Asp Ile Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn Ala Gly Ile
        355                 360                 365

Met Ala Glu Val Glu Glu Leu Arg Lys Arg Val Leu Asp Met Glu Gly
    370                 375                 380

Lys Asp Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp Leu Asn
385                 390                 395                 400

Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys Leu Glu
                405                 410                 415

Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu Glu Asp
            420                 425                 430
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Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys Asn Leu
435 440 445

Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu Glu Ser
450 455 460

Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg Leu Glu
465 470 475 480

Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys Thr Leu
485 490 495

Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys Leu Lys
500 505 510

Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln Val Glu
515 520 525

Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu Thr Lys
530 535 540

Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr Ser Val
545 550 555 560

Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu Glu Glu
565 570 575

Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn Arg Leu
580 585 590

Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys Leu Asn
595 600 605

Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn Asn Lys
610 615 620

Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys Leu Lys
625 630 635 640

Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp Glu Tyr
645 650 655

Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala Gln Phe
660 665 670

Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys Tyr Lys
675 680 685

Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe Lys Arg
690 695 700

Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu Val Asp
705 710 715 720

Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp Leu Ile
725 730 735

Cys His Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys Leu Asn Gln
740 745 750

Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu Asn Leu Thr
755 760 765

Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu Arg Pro Ser
770 775 780

Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys Glu Val
785 790 795 800

Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys Ser Leu Ile
805 810 815

Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu Glu Ser Glu
820 825 830

Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu Ser Phe Lys
835 840 845

Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu Trp Ile Pro
850 855 860

Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys Met Gln Thr
865 870 875 880

Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val Leu Ser His

885 890 895

Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp His Val Gln
900 905 910

Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu Ser Pro His
915 920 925

Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro Lys Gln
930 935 940

Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val Lys Ser Lys
945 950 955 960

Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser Pro Ile
965 970 975

Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser Cys Gly Ser
980 985 990

Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu Ala Val Thr
995 1000 1005

Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu Pro Thr
1010 1015 1020

Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp Arg
1025 1030 1035

Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser
1040 1045 1050

Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser
1055 1060 1065

Pro Tyr Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro
1070 1075 1080

Ser Ala Pro Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly
1085 1090 1095

Ala Leu Asn Lys Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile
1100 1105 1110

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Thr Pro  Thr Ala Thr Pro Leu  Pro Arg Gln Ser Gln  Ile Thr Val
    1115                1120                1125

Ser Asn  Ile Tyr Asn
    1130
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<210> 17
<211> 45
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(45)
<223>

<400> 17
act aaa tca aca aga aaa cag gaa cag aga ttt agg aag aga gat 45
Thr Lys Ser Thr Arg Lys Gln Glu Gln Arg Phe Arg Lys Arg Asp
1 5 10 15

<210> 18
<211> 15
<212> PRT
<213> Homo sapiens

<400> 18

Thr Lys Ser Thr Arg Lys Gln Glu Gln Arg Phe Arg Lys Arg Asp
1 5 10 15

<210> 19
<211> 90
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(90)
<223>

<400> 19
gtg gat gaa cag caa agg ctg acg gca cag ctc acc ctt caa aga cag 48
Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln Arg Gln
1 5 10 15

aaa atc caa gag ctg acc aca aat gca aag gaa aca cat acc 90
Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr
20 25 30

<210> 20
<211> 30
<212> PRT
<213> Homo sapiens

<400> 20

Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln Arg Gln
1 5 10 15

Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr
20 25 30

<210> 21
<211> 1158
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(1158)
<223>

<400> 21

cta aat caa caa gaa aac agg aac aga gat tta gga aga gag att gaa 48
Leu Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu
1 5 10 15

aac ctc act aag gag tta gag agg tac cgg cat ttc agt aag agc ctc 96
Asn Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu
20 25 30

agg cct agt ctc aat gga aga aga att tcc gat cct caa gta ttt tct 144
Arg Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser
35 40 45

aaa gaa gtt cag aca gaa gca gta gac aat gaa cca cct gat tac aag 192
Lys Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys
50 55 60

agc ctc att cct ctg gaa cgt gca gtc atc aat ggt cag tta tat gag 240
Ser Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu
65 70 75 80

gag agt gag aat caa gac gag gac cct aat gat gag gga tct gtg ctg 288
Glu Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu
85 90 95

tcc ttc aaa tgc agc cag tct act cca tgt cct gtt aac aga aag cta 336
Ser Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu
100 105 110

tgg att ccc tgg atg aaa tcc aag gag ggc cat ctt cag aat gga aaa 384
Trp Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys
115 120 125

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atg caa act aaa ccc aat gcc aac ttt gtg caa cct gga gat cta gtc      432
Met Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val
    130                 135                 140

cta agc cac aca cct ggg cag cca ctt cat ata aag gtt act cca gac      480
Leu Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp
145                 150                 155                 160

cat gta caa aac aca gcc act ctt gaa atc aca agt cca acc aca gag      528
His Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu
                165                 170                 175

agt cct cac tct tac acg agt act gca gtg ata ccg aac tgt ggc acg      576
Ser Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr
            180                 185                 190

cca aag caa agg ata acc atc ctc caa aac gcc tcc ata aca cca gta      624
Pro Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val
        195                 200                 205

aag tcc aaa acc tct acc gaa gac ctc atg aat tta gaa caa ggc atg      672
Lys Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met
    210                 215                 220

tcc cca att acc atg gca acc ttt gcc aga gca cag acc cca gag tct      720
Ser Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser
225                 230                 235                 240

tgt ggt tct cta act cca gaa agg aca atg tcc cct att cag gtt ttg      768
Cys Gly Ser Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu
                245                 250                 255

gct gtg act ggt tca gct agc tct cct gag cag gga cgc tcc cca gaa      816
Ala Val Thr Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu
            260                 265                 270

cca aca gaa atc agt gcc aag cat gcg ata ttc aga gtc tcc cca gac      864
Pro Thr Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp
        275                 280                 285

cgg cag tca tca tgg cag ttt cag cgt tca aac agc aat agc tca agt      912
Arg Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser
    290                 295                 300

gtg ata act act gag gat aat aaa atc cac att cac tta gga agt cct      960
Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser Pro
305                 310                 315                 320

tac atg caa gct gta gcc agc cct gtg aga cct gcc agc cct tca gca     1008
Tyr Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro Ser Ala
                325                 330                 335

cca ctg cag gat aac cga act caa ggc tta att aac ggg gca cta aac     1056
Pro Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly Ala Leu Asn
            340                 345                 350
```

aaa aca acc aat aaa gtc acc agc agt att act atc aca cca aca gcc 1104
Lys Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile Thr Pro Thr Ala
355 360 365

aca cct ctt cct cga caa tca caa att aca gtg gaa cca ctt ctt ctg 1152
Thr Pro Leu Pro Arg Gln Ser Gln Ile Thr Val Glu Pro Leu Leu Leu
370 375 380

cct cat 1158
Pro His
385

<210> 22
<211> 386
<212> PRT
<213> Homo sapiens.

<400> 22

Leu Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu
1 5 10 15

Asn Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu
20 25 30

Arg Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser
35 40 45

Lys Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys
50 55 60

Ser Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu
65 70 75 80

Glu Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu
85 90 95

Ser Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu
100 105 110

Trp Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys
115 120 125

Met Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val
130 135 140

Leu Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp

145 150 155 160

His Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu
165 170 175

Ser Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr
180 185 190

Pro Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val
195 200 205

Lys Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met
210 215 220

Ser Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser
225 230 235 240

Cys Gly Ser Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu
245 250 255

Ala Val Thr Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu
260 265 270

Pro Thr Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp
275 280 285

Arg Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser
290 295 300

Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser Pro
305 310 315 320

Tyr Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro Ser Ala
325 330 335

Pro Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly Ala Leu Asn
340 345 350

Lys Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile Thr Pro Thr Ala
355 360 365

Thr Pro Leu Pro Arg Gln Ser Gln Ile Thr Val Glu Pro Leu Leu Leu
370 375 380

Pro His
385

<210> 23
<211> 2355
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(2355)
<223>

<400> 23

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ctg caa gat ata aaa gaa aaa atc agt aag gga gaa tat gga aac gct       48
Leu Gln Asp Ile Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn Ala
1               5                  10                  15

ggt atc atg gct gaa gtg gaa gag ctc agg aaa cgt gtg cta gat atg       96
Gly Ile Met Ala Glu Val Glu Glu Leu Arg Lys Arg Val Leu Asp Met
            20                  25                  30

gaa ggg aaa gat gaa gag ctc ata aaa atg gag gag cag tgc aga gat      144
Glu Gly Lys Asp Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp
        35                  40                  45

ctc aat aag agg ctt gaa agg gag acg tta cag agt aaa gac ttt aaa      192
Leu Asn Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys
    50                  55                  60

cta gag gtt gaa aaa ctc agt aaa aga att atg gct ctg gaa aag tta      240
Leu Glu Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu
65                  70                  75                  80

gaa gac gct ttc aac aaa agc aaa caa gaa tgc tac tct ctg aaa tgc      288
Glu Asp Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys
                85                  90                  95

aat tta gaa aaa gaa agg atg acc aca aag cag ttg tct caa gaa ctg      336
Asn Leu Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu
            100                 105                 110

gag agt tta aaa gta agg atc aaa gag cta gaa gcc att gaa agt cgg      384
Glu Ser Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg
        115                 120                 125

cta gaa aag aca gaa ttc act cta aaa gag gat tta act aaa ctg aaa      432
Leu Glu Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys
    130                 135                 140

aca tta act gtg atg ttt gta gat gaa cgg aaa aca atg agt gaa aaa      480
Thr Leu Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys
145                 150                 155                 160
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tta aag aaa act gaa gat aaa tta caa gct gct tct tct cag ctt caa      528
Leu Lys Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln
                165                 170                 175

gtg gag caa aat aaa gta aca aca gtt act gag aag tta att gag gaa      576
Val Glu Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu
            180                 185                 190

act aaa agg gcg ctc aag tcc aaa acc gat gta gaa gaa aag atg tac      624
Thr Lys Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr
        195                 200                 205

agc gta acc aag gag aga gat gat tta aaa aac aaa ttg aaa gcg gaa      672
Ser Val Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu
    210                 215                 220

gaa gag aaa gga aat gat ctc ctg tca aga gtt aat atg ttg aaa aat      720
Glu Glu Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn
225                 230                 235                 240

agg ctt caa tca ttg gaa gca att gag aaa gat ttc cta aaa aac aaa      768
Arg Leu Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys
                245                 250                 255

tta aat caa gac tct ggg aaa tcc aca aca gca tta cac caa gaa aac      816
Leu Asn Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn
            260                 265                 270

aat aag att aag gag ctc tct caa gaa gtg gaa aga ctg aaa ctg aag      864
Asn Lys Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys
        275                 280                 285

cta aag gac atg aaa gcc att gag gat gac ctc atg aaa aca gaa gat      912
Leu Lys Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp
    290                 295                 300

gaa tat gag act cta gaa cga agg tat gct aat gaa cga gac aaa gct      960
Glu Tyr Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala
305                 310                 315                 320

caa ttt tta tct aaa gag cta gaa cat gtt aaa atg gaa ctt gct aag     1008
Gln Phe Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys
                325                 330                 335

tac aag tta gca gaa aag aca gag acc agc cat gaa caa tgg ctt ttc     1056
Tyr Lys Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe
            340                 345                 350

aaa agg ctt caa gaa gaa gaa gct aag tca ggg cac ctc tca aga gaa     1104
Lys Arg Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu
        355                 360                 365

gtg gat gca tta aaa gag aaa att cat gaa tac atg gca act gaa gac     1152
Val Asp Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp
    370                 375                 380

cta ata tgt cac ctc cag gga gat cac tca gtc ctg caa aaa aaa cta     1200
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Leu Ile Cys His Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys Leu
385                 390                 395                 400

aat caa caa gaa aac agg aac aga gat tta gga aga gag att gaa aac    1248
Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu Asn
                405                 410                 415

ctc act aag gag tta gag agg tac cgg cat ttc agt aag agc ctc agg    1296
Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu Arg
            420                 425                 430

cct agt ctc aat gga aga aga att tcc gat cct caa gta ttt tct aaa    1344
Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys
        435                 440                 445

gaa gtt cag aca gaa gca gta gac aat gaa cca cct gat tac aag agc    1392
Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys Ser
    450                 455                 460

ctc att cct ctg gaa cgt gca gtc atc aat ggt cag tta tat gag gag    1440
Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu Glu
465                 470                 475                 480

agt gag aat caa gac gag gac cct aat gat gag gga tct gtg ctg tcc    1488
Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu Ser
                485                 490                 495

ttc aaa tgc agc cag tct act cca tgt cct gtt aac aga aag cta tgg    1536
Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu Trp
            500                 505                 510

att ccc tgg atg aaa tcc aag gag ggc cat ctt cag aat gga aaa atg    1584
Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys Met
        515                 520                 525

caa act aaa ccc aat gcc aac ttt gtg caa cct gga gat cta gtc cta    1632
Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val Leu
    530                 535                 540

agc cac aca cct ggg cag cca ctt cat ata aag gtt act cca gac cat    1680
Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp His
545                 550                 555                 560

gta caa aac aca gcc act ctt gaa atc aca agt cca acc aca gag agt    1728
Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu Ser
                565                 570                 575

cct cac tct tac acg agt act gca gtg ata ccg aac tgt ggc acg cca    1776
Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro
            580                 585                 590

aag caa agg ata acc atc ctc caa aac gcc tcc ata aca cca gta aag    1824
Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val Lys
        595                 600                 605

tcc aaa acc tct acc gaa gac ctc atg aat tta gaa caa ggc atg tcc    1872
Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser
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    610                 615                 620

cca att acc atg gca acc ttt gcc aga gca cag acc cca gag tct tgt     1920
Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser Cys
625                 630                 635                 640

ggt tct cta act cca gaa agg aca atg tcc cct att cag gtt ttg gct     1968
Gly Ser Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu Ala
                645                 650                 655

gtg act ggt tca gct agc tct cct gag cag gga cgc tcc cca gaa cca     2016
Val Thr Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu Pro
            660                 665                 670

aca gaa atc agt gcc aag cat gcg ata ttc aga gtc tcc cca gac cgg     2064
Thr Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp Arg
        675                 680                 685

cag tca tca tgg cag ttt cag cgt tca aac agc aat agc tca agt gtg     2112
Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser Val
    690                 695                 700

ata act act gag gat aat aaa atc cac att cac tta gga agt cct tac     2160
Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser Pro Tyr
705                 710                 715                 720

atg caa gct gta gcc agc cct gtg aga cct gcc agc cct tca gca cca     2208
Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro Ser Ala Pro
                725                 730                 735

ctg cag gat aac cga act caa ggc tta att aac ggg gca cta aac aaa     2256
Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly Ala Leu Asn Lys
            740                 745                 750

aca acc aat aaa gtc acc agc agt att act atc aca cca aca gcc aca     2304
Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile Thr Pro Thr Ala Thr
        755                 760                 765

cct ctt cct cga caa tca caa att aca gtg gaa cca ctt ctt ctg cct     2352
Pro Leu Pro Arg Gln Ser Gln Ile Thr Val Glu Pro Leu Leu Leu Pro
    770                 775                 780

cat                                                                2355
His
785
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<210> 24
<211> 785
<212> PRT
<213> Homo sapiens

<400> 24

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Leu Gln Asp Ile Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn Ala
1               5                   10                  15
```

```
Gly Ile Met Ala Glu Val Glu Glu Leu Arg Lys Arg Val Leu Asp Met
            20                  25                  30

Glu Gly Lys Asp Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp
        35                  40                  45

Leu Asn Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys
    50                  55                  60

Leu Glu Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu
65                  70                  75                  80

Glu Asp Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys
                85                  90                  95

Asn Leu Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu
            100                 105                 110

Glu Ser Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg
        115                 120                 125

Leu Glu Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys
    130                 135                 140

Thr Leu Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys
145                 150                 155                 160

Leu Lys Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln
                165                 170                 175

Val Glu Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu
            180                 185                 190

Thr Lys Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr
        195                 200                 205

Ser Val Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu
    210                 215                 220

Glu Glu Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn
225                 230                 235                 240
```

```
Arg Leu Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys
                245                 250                 255

Leu Asn Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn
            260                 265                 270

Asn Lys Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys
        275                 280                 285

Leu Lys Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp
    290                 295                 300

Glu Tyr Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala
305                 310                 315                 320

Gln Phe Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys
                325                 330                 335

Tyr Lys Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe
            340                 345                 350

Lys Arg Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu
        355                 360                 365

Val Asp Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp
    370                 375                 380

Leu Ile Cys His Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys Leu
385                 390                 395                 400

Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu Asn
                405                 410                 415

Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu Arg
            420                 425                 430

Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys
        435                 440                 445

Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys Ser
    450                 455                 460

Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu Glu
```

465 470 475 480

Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu Ser
485 490 495

Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu Trp
500 505 510

Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys Met
515 520 525

Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val Leu
530 535 540

Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp His
545 550 555 560

Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu Ser
565 570 575

Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro
580 585 590

Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val Lys
595 600 605

Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser
610 615 620

Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser Cys
625 630 635 640

Gly Ser Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu Ala
645 650 655

Val Thr Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu Pro
660 665 670

Thr Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp Arg
675 680 685

Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser Val
690 695 700

Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser Pro Tyr
705 710 715 720

Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro Ser Ala Pro
725 730 735

Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly Ala Leu Asn Lys
740 745 750

Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile Thr Pro Thr Ala Thr
755 760 765

Pro Leu Pro Arg Gln Ser Gln Ile Thr Val Glu Pro Leu Leu Leu Pro
770 775 780

His
785

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<211> 21
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(21)
<223>

<400> 25
gaa cca ctt ctt ctg cct cat 21
Glu Pro Leu Leu Leu Pro His
1 5

<210> 26
<211> 7
<212> PRT
<213> Homo sapiens

<400> 26

Glu Pro Leu Leu Leu Pro His
1 5

<210> 27
<211> 30
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(30)
<223>

<400> 27
ttg gac aaa gtt gtg gaa aaa cat aaa gaa 30
Leu Asp Lys Val Val Glu Lys His Lys Glu
1 5 10

<210> 28
<211> 10
<212> PRT
<213> Homo sapiens

<400> 28

Leu Asp Lys Val Val Glu Lys His Lys Glu
1 5 10

<210> 29
<211> 30
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(30)
<223>

<400> 29
gag gaa gag cag aag gca acc aga cta gag 30
Glu Glu Glu Gln Lys Ala Thr Arg Leu Glu
1 5 10

<210> 30
<211> 10
<212> PRT
<213> Homo sapiens

<400> 30

Glu Glu Glu Gln Lys Ala Thr Arg Leu Glu
1 5 10

<210> 31
<211> 60
<212> DNA
<213> Homo sapiens

<220>
<221> CDS

<222> (1)..(60)
<223>

<400> 31
ttg gac aaa gtt gtg gaa aaa cat aaa gaa tct tac aga cga atc ctg 48
Leu Asp Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu
1 5 10 15

gga cag ctt tta 60
Gly Gln Leu Leu
20

<210> 32
<211> 20
<212> PRT
<213> Homo sapiens

<400> 32

Leu Asp Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu
1 5 10 15

Gly Gln Leu Leu
20

<210> 33
<211> 150
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(150)
<223>

<400> 33
gtg gat gaa cag caa agg ctg acg gca cag ctc acc ctt caa aga cag 48
Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln Arg Gln
1 5 10 15

aaa atc caa gag ctg acc aca aat gca aag gaa aca cat acc aaa cta 96
Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr Lys Leu
20 25 30

gcc ctt gct gaa gcc aga gtt cag gag gaa gag cag aag gca acc aga 144
Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala Thr Arg
35 40 45

cta gag 150
Leu Glu
50

<210> 34

<211> 50
<212> PRT
<213> Homo sapiens

<400> 34

Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln Arg Gln
1 5 10 15

Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr Lys Leu
20 25 30

Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala Thr Arg
35 40 45

Leu Glu
50

<210> 35
<211> 720
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(720)
<223>

<400> 35
atg cgt tcc aga ggc agt gat acc gag ggc tca gcc caa aag aaa ttt 48
Met Arg Ser Arg Gly Ser Asp Thr Glu Gly Ser Ala Gln Lys Lys Phe
1 5 10 15

cca aga cat act aaa ggc cac agt ttc caa ggg cct aaa aac atg aag 96
Pro Arg His Thr Lys Gly His Ser Phe Gln Gly Pro Lys Asn Met Lys
20 25 30

cat aga cag caa gac aaa gac tcc ccc agt gag tcg gat gta ata ctt 144
His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val Ile Leu
35 40 45

ccg tgt ccc aag gca gag aag cca cac agt ggt aat ggc cac caa gca 192
Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His Gln Ala
50 55 60

gaa gac ctc tca aga gat gac ctg tta ttt ctc ctc agc att ctg gag 240
Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile Leu Glu
65 70 75 80

gga gaa ctg cag gct cga gat gag gtc ata ggc att tta aag gct gaa 288
Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu
85 90 95

```
aaa atg gac ctg gct ttg ctg gaa gct cag tat ggg ttt gtc act cca      336
Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro
            100                 105                 110

aaa aag gtg tta gag gct ctc cag aga gat gct ttt caa gcg aaa tct      384
Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser
        115                 120                 125

acc cct tgg cag gag gac atc tat gag aaa cca atg aat gag ctg gac      432
Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp
    130                 135                 140

aaa gtt gtg gaa aaa cat aaa gaa tct tac aga cga atc ctg gga cag      480
Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln
145                 150                 155                 160

ctt tta gtg gca gaa aaa tcc cat agg caa acc ata ttg gag ttg gag      528
Leu Leu Val Ala Glu Lys Ser His Arg Gln Thr Ile Leu Glu Leu Glu
                165                 170                 175

gaa gaa aag aga aaa cat aaa gaa tac atg gag aag agt gat gaa ttc      576
Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe
            180                 185                 190

ata tgc cta cta gaa cag gaa tgt gaa aga tta aag aag cta att gat      624
Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp
        195                 200                 205

caa gaa atc aag tct cag gag gag aag gag caa gaa aag gag aaa agg      672
Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg
    210                 215                 220

gtc acc acc ctg aaa gag gag ctg acc aag ctg aag tct ttt gct ttg      720
Val Thr Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser Phe Ala Leu
225                 230                 235                 240
```

<210> 36
<211> 240
<212> PRT
<213> Homo sapiens

<400> 36

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Met Arg Ser Arg Gly Ser Asp Thr Glu Gly Ser Ala Gln Lys Lys Phe
1               5                   10                  15

Pro Arg His Thr Lys Gly His Ser Phe Gln Gly Pro Lys Asn Met Lys
            20                  25                  30

His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val Ile Leu
        35                  40                  45

Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His Gln Ala
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50 55 60

Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile Leu Glu
65 70 75 80

Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu
85 90 95

Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro
100 105 110

Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser
115 120 125

Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp
130 135 140

Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln
145 150 155 160

Leu Leu Val Ala Glu Lys Ser His Arg Gln Thr Ile Leu Glu Leu Glu
165 170 175

Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe
180 185 190

Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp
195 200 205

Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg
210 215 220

Val Thr Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser Phe Ala Leu
225 230 235 240

<210> 37
<211> 1152
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(1152)
<223>

<400> 37

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cta aat caa caa gaa aac agg aac aga gat tta gga aga gag att gaa       48
Leu Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu
1               5                  10                  15

aac ctc act aag gag tta gag agg tac cgg cat ttc agt aag agc ctc       96
Asn Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu
            20                  25                  30

agg cct agt ctc aat gga aga aga att tcc gat cct caa gta ttt tct      144
Arg Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser
        35                  40                  45

aaa gaa gtt cag aca gaa gca gta gac aat gaa cca cct gat tac aag      192
Lys Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys
    50                  55                  60

agc ctc att cct ctg gaa cgt gca gtc atc aat ggt cag tta tat gag      240
Ser Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu
65                  70                  75                  80

gag agt gag aat caa gac gag gac cct aat gat gag gga tct gtg ctg      288
Glu Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu
                85                  90                  95

tcc ttc aaa tgc agc cag tct act cca tgt cct gtt aac aga aag cta      336
Ser Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu
            100                 105                 110

tgg att ccc tgg atg aaa tcc aag gag ggc cat ctt cag aat gga aaa      384
Trp Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys
        115                 120                 125

atg caa act aaa ccc aat gcc aac ttt gtg caa cct gga gat cta gtc      432
Met Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val
    130                 135                 140

cta agc cac aca cct ggg cag cca ctt cat ata aag gtt act cca gac      480
Leu Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp
145                 150                 155                 160

cat gta caa aac aca gcc act ctt gaa atc aca agt cca acc aca gag      528
His Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu
                165                 170                 175

agt cct cac tct tac acg agt act gca gtg ata ccg aac tgt ggc acg      576
Ser Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr
            180                 185                 190

cca aag caa agg ata acc atc ctc caa aac gcc tcc ata aca cca gta      624
Pro Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val
        195                 200                 205

aag tcc aaa acc tct acc gaa gac ctc atg aat tta gaa caa ggc atg      672
Lys Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met
    210                 215                 220
```

```
tcc cca att acc atg gca acc ttt gcc aga gca cag acc cca gag tct      720
Ser Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser
225                 230                 235                 240

tgt ggt tct cta act cca gaa agg aca atg tcc cct att cag gtt ttg      768
Cys Gly Ser Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu
                245                 250                 255

gct gtg act ggt tca gct agc tct cct gag cag gga cgc tcc cca gaa      816
Ala Val Thr Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu
            260                 265                 270

cca aca gaa atc agt gcc aag cat gcg ata ttc aga gtc tcc cca gac      864
Pro Thr Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp
        275                 280                 285

cgg cag tca tca tgg cag ttt cag cgt tca aac agc aat agc tca agt      912
Arg Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser
    290                 295                 300

gtg ata act act gag gat aat aaa atc cac att cac tta gga agt cct      960
Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser Pro
305                 310                 315                 320

tac atg caa gct gta gcc agc cct gtg aga cct gcc agc cct tca gca     1008
Tyr Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro Ser Ala
                325                 330                 335

cca ctg cag gat aac cga act caa ggc tta att aac ggg gca cta aac     1056
Pro Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly Ala Leu Asn
            340                 345                 350

aaa aca acc aat aaa gtc acc agc agt att act atc aca cca aca gcc     1104
Lys Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile Thr Pro Thr Ala
        355                 360                 365

aca cct ctt cct cga caa tca caa att aca gta agt aat ata tat aac     1152
Thr Pro Leu Pro Arg Gln Ser Gln Ile Thr Val Ser Asn Ile Tyr Asn
    370                 375                 380
```

<210> 38
<211> 384
<212> PRT
<213> Homo sapiens

<400> 38

```
Leu Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu
1               5                   10                  15

Asn Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu
            20                  25                  30

Arg Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser
```

```
      35                  40                  45

Lys Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys
    50                  55                  60

Ser Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu
65                  70                  75                  80

Glu Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu
                85                  90                  95

Ser Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu
            100                 105                 110

Trp Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys
        115                 120                 125

Met Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val
    130                 135                 140

Leu Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp
145                 150                 155                 160

His Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu
                165                 170                 175

Ser Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr
            180                 185                 190

Pro Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val
        195                 200                 205

Lys Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met
    210                 215                 220

Ser Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser
225                 230                 235                 240

Cys Gly Ser Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu
                245                 250                 255

Ala Val Thr Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu
            260                 265                 270
```

```
Pro Thr Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp
        275                 280                 285

Arg Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser
    290                 295                 300

Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser Pro
305                 310                 315                 320

Tyr Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro Ser Ala
                325                 330                 335

Pro Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly Ala Leu Asn
            340                 345                 350

Lys Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile Thr Pro Thr Ala
        355                 360                 365

Thr Pro Leu Pro Arg Gln Ser Gln Ile Thr Val Ser Asn Ile Tyr Asn
    370                 375                 380
```